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Abstract—Hypertension (HTN) is a major risk factor for intracranial hemorrhage. We, therefore, investigated the prevalence, treatment, and control of HTN in adult patients with hemophilia (PWH). PWH≥18 years (n=458) from 3 geographically different cohorts in the United States were evaluated retrospectively for HTN and risk factors. Results were compared with the nationally representative sample provided by the contemporary National Health and Nutrition Examination Survey (NHANES). PWH had a significantly higher prevalence of HTN compared with NHANES. Overall, the prevalence of HTN was 49.1% in PWH compared with 31.7% in NHANES. At ages 18 to 44, 45 to 64, 65 to 74, and ≥75 years, the prevalence of HTN for PWH was 31.8%, 72.6%, 89.7%, and 100.0% compared with 12.5%, 41.2%, 64.1%, and 71.7% in NHANES, respectively. Of treated hypertensive PWH, only 27.1% were controlled, compared with 47.7% in NHANES (all *P*<0.05). Age, body mass index, diabetes mellitus, and renal function were independently associated with HTN. Among patients with moderate or severe hemophilia there was a trend (≈1.5-fold) for higher odds of having HTN compared with patients with mild hemophilia. On the basis of these results, new care models for adult PWH and further studies for the causes of HTN in hemophilia are recommended. (*Hypertension.* 2013;62:209-215.) ● Online Data Supplement

Key Words: BP ■ cardiovascular disease risk factors ■ hemophilia ■ hypertension ■ NHANES ■ prevalence

Hemophilia is an X-linked bleeding disorder character-ized by deficiencies of Factor VIII or IX. With the advent of safe clotting factor preparations, most of those born with hemophilia survive into adulthood free of HIV. As such, almost half of the ≈20 000 patients with hemophilia (PWH) living in the United States are now adults.[1]

Based primarily on previous European studies that reported lower cardiovascular disease (CVD) mortality for PWH compared with age- and sex-matched nonhemophiliacs, CVD prevention in hemophilia has received little attention because of the perception that PWH are protected from CVD attributable to hypocoagulability.[2–4] Additionally, life-threatening viral diseases dominated care and PWH died young (median age at death, 40.5–46 years; 1987–1998[5]). Recently, cardiovascular care for those with hemophilia has gained new attention because, at least in the United States, PWH were demonstrated to have twice the prevalence of symptomatic CVD and 3-fold higher mortality rates from CVD than normal age-matched men, which included intracranial hemorrhage (ICH).[6,7] Because hemophilia is a rare disease, the incidence of ICH is mostly provided by event per 10^5 patient years, whereas ICH incidence in the normal population is mostly provided per 10^5 subjects during a given time period (often as annual rate). Estimates of the absolute frequency of ICH in PWH are 290 to 748 per 10^5 patient years,[8,9] and comparatively this is estimated to be 20 to 50 times more frequent than in the normal population (≈13–40 per 10^5 patient years).[8,10,11] ICH is the most severe bleeding event and leading cause of death in PWH[5,12] and carries a high mortality rate. Patients with severe or mild/moderate hemophilia have standard mortality ratios for ICH that are ≈40- and 9-fold higher, respectively, than for normal age-matched men.[13] The most significant risk factor for ICH in the normal population is hypertension (HTN),[13–17] and HTN was also the most frequent comorbidity in a recent investigation of ICH in Italian PWH.[18] Notably, in the general population every 20-point mm Hg increase in systolic blood pressure (BP), or 10-point mm Hg increase in diastolic BP, is associated with a 2-fold increased risk of ICH.[14,15] Hence, it is concerning that little is currently known about the prevalence and severity of HTN in PWH. There is emerging evidence from Europe that the prevalence of HTN in PWH may be increased compared with the normal population or age-matched men, but evidence remains controversial. That is, studies are either small or based on patients from ethnically uniform Northern European cohorts.[3,19,21]

Hence, investigating HTN in hemophilia is highly relevant. Here, we report the prevalence and control of HTN, as well

as risk factors associated with this condition, from a retrospective analysis of 3 cohorts with hemophilia located in geographically different areas of the United States. Findings were compared with the general population by comparing with contemporary data from the National Health and Nutrition Examination Survey (NHANES).

Materials and Methods

Participants

A retrospective data collection was performed for all male PWH (n=458) aged ≥18 years visiting 3 Hemophilia Treatment Centers in the United States: University of California San Diego (UCSD), Tulane University (TU), and the Los Angeles Orthopaedic Hospital (LAOH). Data were extracted manually from the electronic medical record and paper charts. Record date ranges were 2004–2012 for UCSD, 2008–2011 for TU, and 2005–2012 for LAOH. Patient confidentiality safeguards and data acquisition methods were approved by the Human Research Protection Programs of all 3 institutions.

Health History

Data extracted included demographic information on age, ethnicity, hemophilia type and severity, positive tests for Hepatitis C or HIV by serology or reported history thereof, medication history, prior diagnosis of HTN and smoking status. Inhibitors (neutralizing antibodies against Factor VIII or Factor IX) were documented as present if the patient was positive for inhibitors at any of the recorded BP measurements.

Physical Measurements

Data extracted included laboratory parameters pertaining to diabetes mellitus (Hemoglobin A1c, random blood glucose) and serum creatinine. Laboratory values at all centers were obtained nonfasting during regular health visits. The diagnosis of diabetes mellitus was defined according to the 2010 American Diabetes Association Standards of Medical Care in Diabetes as medication use for glycemic control, Hemoglobin A1c>6.5, or presence of ≥2 random glucose levels >200 mg/dL.[22] Renal function was determined by estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[23] Age, BMI (weight [kg]/height [m²]), and creatinine at last recorded blood pressure were used for analysis.

BP in all clinics was measured in accordance with the current recommendations of the American Heart Association.[24] In brief, BPs were obtained by licensed staff using calibrated automated manometers with subjects in a chair at rest, arm supported at heart level. All records included ≥1 recorded BP and no patient was excluded from analysis. The 3 most recent BP measurements were used to evaluate HTN status (mean number of measurements was 2.6, 2.4, and 2.9 for UCSD, TU, and LAOH, respectively). HTN was defined as prior physician diagnosis of HTN and use of antihypertensive medication, or ≥2 elevated BP measurements (systolic BP, ≥140 mm Hg or diastolic BP, ≥90 mm Hg). Treated HTN was defined as reported use of antihypertensive medication during the last year of the study period. Controlled HTN was defined as a treated systolic BP <140 mm Hg and diastolic BP <90 mm Hg. For the assessment of controlled HTN, the most recent BP measurements during the last year of the study period were used.

Statistical Analysis

All statistical analyses were performed using SAS Version 9.2 (Cary, NC). Differences in demographic and health characteristics were evaluated with *t* tests or Wilcoxon Mann–Whitney for continuous variables and χ^2 tests for categorical variables across treatment centers and HTN classification.

Overall and age-based prevalence of HTN in the study cohorts was compared with the prevalence of HTN for men in published data from NHANES.[25] NHANES is a complex, multistage probability sample that represents a statistical model of the entire civilian noninstitutionalized US population conducted by the Centers for Disease Control and Prevention National Center for Health Statistics (National Health and Nutrition Examination Survey Data, Hyattsville, MD: US Department of Health and Human Services, CD, 2010; available at http://www.cdc.gov/nchs/nhanes.htm). NHANES HTN was defined as elevated BP (average of ≤3 BP measurements, obtained under standard conditions during a single physical examination at the mobile examination center) or report of use of antihypertensive medication (home health interview). One-sample binomial proportion tests were used to test the equality of HTN prevalence and HTN control in both cohorts.

Logistic regression was used to evaluate the associations of known risk factors with HTN. Characteristics with *P*<0.20 in univariate analysis were included in the multivariate logistic regression analyses for determination of independent predictors of HTN. An initial model included only hemophilia type and severity. A second model additionally adjusted for age, race, and treatment center, and a final model additionally adjusted for traditional risk factors (smoking history, diabetes mellitus, eGFR, and BMI). Effect modification of the association of hemophilia severity with HTN was evaluated by multiplicative interaction terms within the adjusted models. *P*<0.05 were considered statistically significant for all analyses, including interactions. Nonsignificant interactions were not included in final models.

Results

Basic Cohort Characteristics

Male patients aged ≥18 years seen at UCSD (n=114), TU (n=120), and LAOH (n=224) were included in the retrospective analysis. The characteristics of the 3 cohorts are described in Table 1. The cohorts were not homogeneous and differed by mean age, ethnic composition, inhibitor status, severity of hemophilia, smoking status, hepatitis C, and median creatinine. Conversely, the cohorts were similar on the proportion of patients with hemophilia A or B, mean BMI, mean eGFR, HIV status, and prevalence of diabetes mellitus.

Prevalence of HTN, Treatment and Control in PWH

There were no statistical differences in the overall or age-stratified prevalences of HTN among the 3 cohorts (45.6% UCSD, 46.7% TU, and 52.2% LAOH; *P*=0.42; all *P*>0.05). Also, there were no differences between percent patients treated for HTN in each cohort (29.8 in UCSD, 20% in TU, 26.3% LAOH; *P*=0.21). Table 2 shows the details of BP collection (date ranges and mean number of measurements) across the cohorts and the prevalence of HTN overall and according to age group (aged 18–44, 45–64, 65–74, and ≥75 years) by geographic cohort.

The prevalence of HTN for all age groups combined (PWH, n=458), and separated by age group or ethnicity was compared with NHANES (Figure 1A and 1B). The overall prevalence of HTN was significantly higher in PWH (49.1%) than NHANES (31.7%; *P*<0.0001). At ages 18 to 44, 45 to 64, 65 to 74, and ≥75 years, the prevalence of HTN for PWH was 31.8%, 72.6%, 89.7%, and 100.0% compared with 12.5%, 41.2%, 64.1%, and 71.7% in NHANES, respectively (all *P*≤0.05). PWH HTN prevalence was significantly higher than NHANES among whites (33.7% versus 49.1%) and Hispanics (19.9% versus 39.1%; *P*≤0.05) and not significantly different among blacks (37.6%, 48.0%; *P*=0.06).

Next, the subject characteristics were analyzed by HTN status in univariate analysis (Table S1 in the online-only Data Supplement). Patients with hemophilia with HTN were significantly older (mean age, 48.3 versus 34.4 years; *P*<0.0001), had higher BMI (mean BMI, 28.2 versus 26.2; *P*=0.0005), higher creatinine values (median, 0.90 versus 0.83 mg/mL; *P*=0.002),

Table 1.   Baseline Cohort Characteristics

Cohort	UCSD	TU	LAOH	P Value
No. of patients	114	120	224	
Mean age	41.3±14.5	37.5±13.5	43.2±15.5	0.003
Race				<0.0001
White	56 (49.1%)	84 (70.0%)	103 (45.8%)	
Black	11(9.7%)	25 (20.8%)	14 (6.2%)	
Hispanic	31(27.2%)	1(0.8%)	78 (34.7%)	
Other	16 (14.0%)	10 (8.3%)	30 (13.3%)	
Hemophilia				0.44
A	90 (79.0%)	89 (74.2%)	183 (81.3%)	
B	24 (21.0%)	31(25.8%)	41(18.2%)	
Unknown	0	0	1(0.4%)	
Inhibitor				<0.0001
Positive	4 (3.5%)	17 (14.2%)	8 (3.6%)	
Negative	70 (61.4%)	103 (85.8%)	207 (92.0%)	
Not tested	40 (35.1%)	0	10 (4.4%)	
Severity				<0.0001
Severe	50 (43.9%)	69 (57.5%)	134 (59.6%)	
Moderate	17 (14.9%)	30 (25.0%)	17 (7.8%)	
Mild	46 (40.4%)	21 (17.5%)	66 (29.3%)	
Unknown	1 (0.9%)	0	8 (3.6%)	
HIV status				<0.0001
Positive	27 (23.7%)	20 (16.7%)	58 (25.8%)	
Negative	62 (54.4%)	93 (77.5%)	167 (74.2%)	
Not tested	25 (21.9%)	7 (5.8%)	0	
Hepatitis C				<0.0001
Positive	62 (54.4%)	71(59.2%)	168 (74.7%)	
Negative	38 (33.3%)	45 (37.5%)	54 (24.0%)	
Not tested	14 (12.3%)	4 (3.3%)	3 (1.3%)	
Mean BMI	27.9±6.6	27.1±5.3	26.9±5.7	0.31
Smoking				<0.0001
Ever	20 (16.8%)	40 (33.3%)	54 (34.2%)	
Never	99 (83.2%)	80 (66.7%)	91(57.6%)	
Unknown	…	…	13 (8.2%)	
Diabetes mellitus				0.17
Yes	7 (6.1%)	5 (4.2%)	24 (10.7%)	
No	107 (93.9%)	115 (95.8%)	200 (88.9%)	
Unknown	0	0	1 (0.4%)	
Median, creatinine (mg/mL)	0.84 (0.22)	0.90 (0.30)	0.80 (0.30)	0.0002
Mean, eGFR (mL/min per 1.73 m²)	106.3±21.7	101.9±25.2	102.1±24.6	0.28

BMI indicates body mass index; eGFR, estimated glomerular filtration rate; LAOH, Los Angeles Orthopedic Hospital; TU, Tulane University; and UCSD, University of California San Diego.

and lower eGFR (mean eGFR, 94.4 versus 112.0 mL/min per 1.73 m²; $P<0.0001$). The prevalence of diabetes mellitus (13.8% versus 1.7%; $P<0.001$) was significantly higher in patients with HTN. Hepatitis C and hemophilia severity also differed according to HTN status. There were no differences in ethnicity, ever smoking, or HIV status.

Compared with published results from NHANES,[25] control of HTN was significantly lower among PWH. That is, of treated hypertensive PWH, only 27.1% were controlled, compared with 47.7% in NHANES ($P<0.0001$; Figure 2A). For PWH seen at UCSD, detailed treatment records were available for data review. Analysis of control during the 2 years preceding database closure revealed a significant increase of HTN control of PWH between 2010 and 2012 because of healthcare provider awareness. These records indicated that HTN control increased from 1% to 36.5%, 2010–2012. These percentages are similar to NHANES, where 47.7% of treated individuals are controlled (Figure 2B).

Table 2.   Prevalence of Hypertension and Hypertension Treatment in Patients With Hemophilia

Blood Pressure	UCSD	TU	LAOH	P Value
Collection date range	2004–2012	2008–2011	2005–2012	
Mean collected (±SD)	2.6±0.7	2.4±0.8	2.9±0.3	
Prevalence of HTN				
Overall	52/114 (45.6%)	56/120 (46.7%)	117/224 (52.2%)	0.42
18–44 y	17/68 (25.0%)	32/88 (36.4%)	41/127 (32.3%)	0.32
45–64 y	23/33 (69.7%)	19/27 (70.4%)	56/75 (74.7%)	0.83
65–74 y	11/12 (91.7%)	3/3 (100%)	12/14 (85.7%)	0.73
≥75 y	1/1 (100%)	2/2 (100%)	8/8 (100%)	…
Treated HTN	34/114 (29.8%)	24/120 (20.0%)	59/224 (26.3%)	0.21

HTN indicates hypertension; LAOH, Los Angeles Orthopedic Hospital; TU, Tulane University; and UCSD, University of California San Diego.

Independent Risk Factors of HTN in Hemophilia

Table 3 shows the association of risk factors with HTN among PWH. Compared with hemophilia A and in unadjusted analyses, patients with hemophilia B had a 1.87-fold higher odds of HTN ($P=0.009$) that was attenuated and no longer significant once adjusted for age, race, treatment center (model 2; odds ratio [OR], 1.36; $P=0.27$), and traditional risk factors (model 3; OR, 1.63; $P=0.11$). Compared with patients with mild hemophilia and after adjustment for age, race, and treatment center (model 2), patients with moderate/severe hemophilia had a 1.3-fold higher odds of HTN ($P=0.32$). After further adjustment for traditional risk factors (model 3), this association increased to a 1.51-fold higher odds ($P=0.15$). In the fully adjusted model,

higher age (OR, 1.36 per 5 years; $P<0.0001$), higher BMI (OR, 1.60 per 5 kg/m^2; $P<0.0001$), and the presence of diabetes mellitus (OR, 3.96; $P=0.05$) were associated with higher odds of HTN, whereas a higher eGFR (OR, 0.83 per mL/min per 1.73 m^2; $P=0.02$) was associated with a decreased odds for HTN. Model 3 was repeated with log-transformed creatinine level in place of eGFR. Higher creatinine level (OR, 4.43 per log mg/dL; $P=0.009$) was associated with increased odds for HTN, whereas all other associations were unchanged.

Discussion

Using a relatively large retrospective analysis, our results indicate that adult PWH who were aged ≥18 years and from 3 geographically distinct areas in North America have a significantly higher prevalence of HTN compared with the general male population represented by NHANES. The increased prevalence of HTN was evident at all ages. Our study populations were ethnically diverse, with ≈30% PWH of Hispanic ethnicity in California and ≈20% PWH of black ethnicity in Louisiana. The high prevalence of HTN was evident across all ethnicities, but not significant for blacks, likely because of small sample size. Also, HTN was independently associated with age, presence of diabetes mellitus, BMI, and renal function by creatinine and eGFR. There was also a trend for HTN with more severe stages of hemophilia (plasma clotting factor activity ≤5% [severe and moderate hemophilia combined]) compared with mild hemophilia (plasma clotting factor activity >5%). Of concern, control of HTN was significantly less than that reported for the general male population. These findings are important and clinically relevant because the HTN of hemophilia may be a serious under-recognized entity, requiring new care models.

An unexplained association between hemophilia and HTN was described in a Dutch cohort as early as the 1980s[3] and more recently in a contemporary Northern European cohort by Fransen van de Putte et al.[21] This cohort, including ≈700 PWH (mean age 49.8 years), also exhibited a significantly higher prevalence of HTN in PWH compared with normal men in National Health Registries. Similar to our study, HTN was higher in patients with severe hemophilia than in those with nonsevere hemophilia, similar for hemophilia A and B, associated with BMI and age, and not associated with HIV. Different from our study results there was no association of HTN with renal function or hepatitis C. However, renal
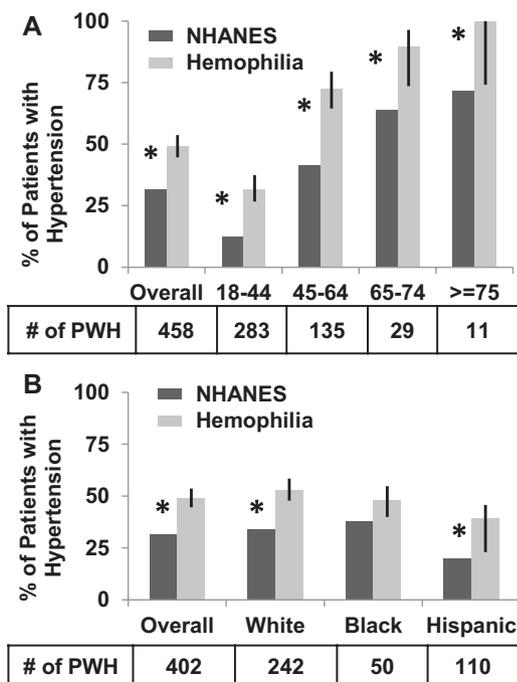
Figure 1. The prevalence of hypertension in patients with hemophilia is significantly higher compared with the general population. The prevalence of hypertension for patients with hemophilia (PWH) was compared by 1 sample binomial test with male National Health and Nutrition Examination Survey (NHANES) data for all age groups combined (overall), and divided into different age groups (**A**) and into matching ethnic groups (**B**; only white, black, and Hispanic included in NHANES); *$P≤0.5$. Error bars indicate 95% confidence intervals.
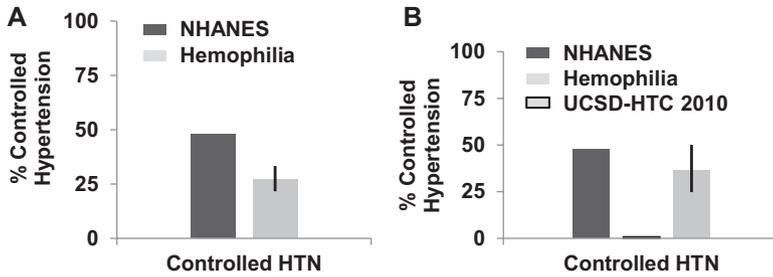
Figure 2. The control of hypertension (HTN) in patients with hemophilia (PWH) is significantly lower compared with the general male population. **A**, Percent control of treated PWH from all 3 study cohorts combined was compared by 1 sample binomial test with published male National Health and Nutrition Examination Survey (NHANES) data. Percent control was significantly lower for PWH than males from NHANES. **B**, For the Hemophilia Treatment Center (HTC) at University of California San Diego (UCSD), detailed information on control was available for each year of retrospective analysis. Analysis of control during the 2 years preceding database closure revealed a significant increase of HTN control of PWH between 2010 and 2012 because of healthcare provider awareness. These data suggest that HTN of hemophilia can be controlled with usual antihypertensives; *$P \leq 0.5$. Error bars indicate 95% confidence intervals.

function in the European study was based on creatinine alone, which may be less sensitive than renal function estimates by eGFR. Results from 2 other contemporary Dutch and Italian case–control studies also support that the prevalence of HTN may be higher in adult PWH compared with age-matched men. Biere-Rafi et al[19] demonstrated that the prevalence of HTN was 51% in PWH (n=100; mean age, 47 years) compared with 37% (*P*=0.03) in normal men and Siboni et al[20] demonstrated similar findings for 35 elderly PWH (≥65 years). Because it was felt that these studies were too small for definite conclusions,[21] and because other studies evaluating (cardiovascular) health parameters in PWH did not find an increased prevalence of HTN,[26–28] controversy remained.[21] Our study is to the best of our knowledge the first in North America to specifically examine the prevalence of HTN and associated risk factors in PWH, and to report an increased prevalence of HTN in PWH.

As expected, the prevalence of HTN increased with age for study participants of NHANES and for PWH. There were relatively fewer numbers of PWH in the older age groups. The attrition may largely be explained by early death either because of lack of clotting factor preparations before the 1970s or to viral infections through contaminated clotting factor preparations provided before the mid-1980s.[2] However, the contribution of premature death because of other events in hemophilia, such as catastrophic bleeding, is currently unclear. Notably, patients with moderate and severe hemophilia (plasma clotting factor levels, <5%) had a ≈1.5-fold higher odds of HTN compared with patients with mild hemophilia (plasma clotting factor levels, 6% to 50%) when adjusted for additional risk factors. Although this trend was not statistically significant, it may be considered clinically meaningful, especially because similar findings were present in the European cohort.[21] The lack of

Table 3.   Independent Risk Factors for Hypertension in Hemophilia in a Multistage Model Including Patient Nonmodifiable Risk Factors (Model 2) and Patient Modifiable Risk Factors (Model 3)

Risk Factors	Model 1	Model 2	Model 3
Age, per 5 y	…	1.48 (1.35;1.62); <0.0001	1.36 (1.201.53); <0.0001
Race			
White	…	Ref	Ref
Black	…	0.86 (0.43;1.75); 0.68	0.52 (0.24;1.15); 0.11
Hispanic	…	0.91 (0.50;1.64); 0.75	0.63 (0.32;1.22); 0.17
Other	…	1.22 (0.61;2.41); 0.58	1.09(0.53;2.23); 0.82
Center			
LAOH	…	Ref	Ref
UCSD	…	0.89 (0.52;1.51); 0.66	0.88 (0.49;1.57); 0.66
TU	…	1.18 (0.67;2.09); 0.56	1.26 (0.66;2.38); 0.48
BMI, per 5 kg/m^2	…	…	1.60 (1.28;1.99); <0.0001
Ever smoker	…	…	1.28 (0.76;2.13); 0.35
Diabetes mellitus	…	…	3.96 (1.01;15.56); <0.05
eGFR, per mL/min per 1.73 m^2	…	…	0.83 (0.71;0.96); 0.02
Hemophilia type			
A	Ref	Ref	Ref
B	1.87 (1.17;2.98); 0.009	1.36 (0.79;2.32); 0.27	1.63 (0.90;2.94); 0.11
Severity			
Mild	Ref	Ref	Ref
Moderate/severe	0.87 (0.57;1.32); 0.51	1.30 (0.78;2.18); 0.32	1.51 (0.86;2.67); 0.15

BMI indicates body mass index; eGFR, estimated glomerular filtration rate; LAOH, Los Angeles Orthopedic Hospital; TU, Tulane University; and UCSD, University of California San Diego.

significance may be because of sample size effect, or possibly by survival bias in patients with severe hemophilia and HTN resulting in their early attrition. When patients were categorized into severe versus nonsevere hemophilia, no such trend was observed (data not shown), suggesting a threshold effect around moderate hemophilia in association with HTN. In general, one may speculate that HTN in patients with more severe bleeding phenotypes (such as moderate and severe hemophilia) may be influenced by their limited ability for vigorous exercise and by forced sedentary lifestyle because of bleeding risk. However, our study is limited by the ability to provide insights on diet, exercise, hyperlipidemia (consistent collection of fasting lipid panels was not uniformly performed at all centers), or obstructive sleep apnea. Also, our study lacks information on renal bleeding or intermittent renal (micro)bleeding (which can only be reasonably ascertained by frequent urinalyses), as well as clotting factor usage and history of previously eradicated inhibitors. Inhibitors mostly occur in patients with severe hemophilia and may influence vascular health (eg, through immune complex formation). Also, our comparator group was not made up of chronically ill patients or patients with regular clinic visits. Hence, the observed higher prevalence of HTN between PWH and the controls may have been the result of the regular clinic visits of PWH, where HTN may be more readily diagnosed and more BP measurements are available to make the diagnosis. Conversely, single visits for BP measurements as in NHANES or other National Health Registries may either over- or underestimate the prevalence of HTN in the general population. However, the highly significant differences between PWH and normal men for all age and ethnic groups in our study are highly suggestive of HTN of hemophilia. By not having home BP readings, we were not able to discern a white-coat HTN effect in PWH or NHANES. However, one may think that white-coat effects in PWH presenting regularly to a tertiary clinic focused on bleeding complications as opposed to emphasizing BP control in a primary care setting is unlikely. In general, it should be kept in mind that white-coat HTN is not a benign condition and has been associated previously with a higher incidence of stroke.[29] PWH were not entirely comparable with the NHANES study population with respect to prevalence of traditional risk factors for HTN, such as diabetes mellitus, obesity, renal function, or smoking.[30–34] Specifically, although the mean BMI and prevalence of diabetes mellitus were similar between the 2 groups,[30,32,33] PWH had a higher prevalence of never smokers (≈40% NHANES versus ≈66% PWH)[31] and a lower prevalence of renal disease (eGFR<60 mL/min per 1.73 m²: ≈12% NHANES versus ≈5% PWH [data not shown]).[34]

Our results suggest that traditional risk factors alone are unlikely to explain the higher prevalence of HTN in PWH, although interactions between these risk factors and hemophilia status cannot be entirely ruled out. Currently, reasons for the high prevalence of HTN in PWH remain unclear. Potential molecular mechanisms could be both of (epi)genetic or hemostatic origin. Interactions of hemostatic factors with the vessel wall or impact of chronic attenuation of hemostasis on mechanisms regulating vascular tone and endothelial relaxation are conceivable. For instance, decreased thrombin formation influencing activation of thrombin substrates, levels of activated protein C, and activated thrombin activatable fibrinolysis inhibitor may affect BP regulation.[35–37] Although less likely because of the >1000 different mutations described to date causing hemophilia (hadb. org.uk; factorix.org), genetic predisposition associated with the mutational hemophilia defect on the X-chromosome cannot be excluded to predispose PWH to HTN.

Perspective

From a pragmatic clinical stand point, our findings may have immediate consequences for hemophilia care. New paradigms to include HTN control seem necessary. PWH are at extreme risk of mortality from ICH[13] and the 2 most significant risk factors for ICH are age and HTN.[38,39] It is concerning that HTN went unrecognized, untreated, and uncontrolled in many patients at all 3 Hemophilia Treatment Centers, probably representing general hemophilia care patterns in the United States. As evidenced at the UCSD Hemophilia Treatment Center, healthcare provider awareness and effort can increase HTN control to what is reported for the general population. And, the HTN of hemophilia seems treatable with usual antihypertensives.

Given that hemophilia is a rare disease, current studies are exploratory and limited by the small number of patients. However, our study results provide evidence that the HTN of hemophilia is an important comorbidity, present even at young ages, across continents and ethnicities. In addition to informing medical practice, we hope that our findings will stimulate basic research addressing pathogenesis, such as the effects of altered hemostasis or genetic associations. In addition, prospective studies of traditional risk factors and variables, such as history of inhibitors, clotting factor consumption, diet, exercise, pain level, inflammation, renal bleeding, or bleeding phenotypes, are required to improve our understanding of this condition.

Disclosures

None.

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Novelty and Significance

What Is New?

- This study demonstrates for the first time that adult patients with hemophilia living in North America have a higher prevalence of hypertension that is present across all ethnicities and inadequately recognized and controlled compared with the general population in the United States.

What Is Relevant?

- Hypertension is a risk factor for intracerebral hemorrhage. Current care paradigms at comprehensive hemophilia treatment centers do not usually include hypertension control and need to be adapted because patients with hemophilia are at high risk for intracranial hemorrhage with a high fatality rate.

Summary

Adult patients with hemophilia have a high prevalence of hypertension, and the hypertension remains often unrecognized and uncontrolled. These findings suggest the inclusion of cardiovascular preventive measures at comprehensive hemophilia treatment centers.

Prevalence and Risk Factors for Hypertension in Hemophilia

Online Supplemental Data Table

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Table S1.
Univariate Risk Analysis for Hypertension (HTN)

Risk Factors	No HTN (n=233)	HTN (n=225)	p-value
Age, years	34.4 ± 10.8	48.3 ± 15.3	**<.0001**
Ethnicity, n (%)			.10
White	114 (48.9%)	128 (56.9%)	
Black	26 (11.2%)	24 (10.7%)	
Hispanic	67 (28.8%)	43 (19.1%)	
Other	26 (11.2%)	30 (13.3%)	
BMI, kg/m^2	26.2 ± 5.5	28.2 ± 6.0	**.0005**
Ever Smoker, n (%)	62 (26.6%)	75 (33.3%)	.06
Diabetes, n (%)	4 (1.7%)	31 (13.8%)	**<.0001**
Creatinine	0.83 (0.26)	0.90 (0.20)	**.002**
eGFR, mL/min/1.73m^2	112.0 ± 18.2	94.4 ± 25.9	**<.0001**
HIV, n (%)			.20
Not Tested	18 (7.7%)	14 (6.2%)	
Positive	45 (19.3%)	59 (26.2%)	
Negative	170 (73.0%)	152 (67.6%)	
HepC positive, n (%)			.006
Not Tested	11 (4.7%)	10 (4.4%)	
Positive	137 (58.8%)	163 (72.4%)	
Negative	85 (36.5%)	52 (23.1%)	
Hemophilia Severity, n (%)			.0004
Mild	64 (27.5%)	70 (31.1%)	
Moderate	23 (9.9%)	49 (21.8%)	
Severe	146 (62.7%)	106 (42.1%)	

eGFR = estimated Glomerular Filtration Rate; BMI = Body mass Index; HepC = Hepatitis C