Hemophilia and Hypertension

Prevalence and Risk Factors for Hypertension in Hemophilia

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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.)

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

Hemophilia is an X-linked bleeding disorder characterized 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 ≈ 200000 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 who 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).5,6 Because hemophilia is a rare disease, the incidence of ICH is mostly provided by event per 107 patient years, whereas ICH incidence in the normal population is mostly provided per 107 subjects during a given time period (often as annual rate). Estimates of the absolute frequency of ICH in PWH are 290 to 748 per 105 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 105 patient years).10,11 ICH is the most severe bleeding event and leading cause of death in PWH12 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 mmHg increase in systolic blood pressure (BP), or 10-point mmHg 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.5,19,20

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.2 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 mmHg or diastolic BP ≥90 mmHg). 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 mmHg and diastolic BP <90 mmHg. 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 χ² 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

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),...
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 1. Baseline Cohort Characteristics

<table>
<thead>
<tr>
<th>Cohort</th>
<th>UCSD</th>
<th>TU</th>
<th>LAOH</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>114</td>
<td>120</td>
<td>224</td>
<td>0.003</td>
</tr>
<tr>
<td>Mean age</td>
<td>41.3±14.5</td>
<td>37.5±13.5</td>
<td>43.2±15.5</td>
<td>0.003</td>
</tr>
<tr>
<td>Race</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>56 (49.1%)</td>
<td>84 (70.0%)</td>
<td>103 (45.8%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>11 (9.7%)</td>
<td>25 (20.8%)</td>
<td>14 (6.2%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>31 (27.2%)</td>
<td>1 (0.8%)</td>
<td>78 (34.7%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>16 (14.0%)</td>
<td>10 (8.3%)</td>
<td>30 (13.3%)</td>
<td></td>
</tr>
<tr>
<td>Hemophilia</td>
<td>0.44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>90 (79.0%)</td>
<td>89 (74.2%)</td>
<td>183 (81.3%)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>24 (21.0%)</td>
<td>31 (25.8%)</td>
<td>41 (18.2%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>0</td>
<td>1 (0.4%)</td>
<td></td>
</tr>
<tr>
<td>Inhibitor</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>4 (3.5%)</td>
<td>17 (14.2%)</td>
<td>8 (3.6%)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>70 (61.4%)</td>
<td>103 (85.8%)</td>
<td>207 (92.0%)</td>
<td></td>
</tr>
<tr>
<td>Not tested</td>
<td>40 (35.1%)</td>
<td>0</td>
<td>10 (4.4%)</td>
<td></td>
</tr>
<tr>
<td>Severity</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>50 (43.9%)</td>
<td>69 (57.5%)</td>
<td>134 (59.6%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>17 (14.9%)</td>
<td>30 (25.0%)</td>
<td>17 (7.8%)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>46 (40.4%)</td>
<td>21 (17.5%)</td>
<td>66 (29.3%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (0.9%)</td>
<td>0</td>
<td>8 (3.6%)</td>
<td></td>
</tr>
<tr>
<td>HIV status</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>27 (23.7%)</td>
<td>20 (16.7%)</td>
<td>58 (25.8%)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>62 (54.4%)</td>
<td>93 (77.5%)</td>
<td>167 (74.2%)</td>
<td></td>
</tr>
<tr>
<td>Not tested</td>
<td>25 (21.9%)</td>
<td>7 (5.8%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>62 (54.4%)</td>
<td>71 (59.2%)</td>
<td>168 (74.7%)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>38 (33.3%)</td>
<td>45 (37.5%)</td>
<td>54 (24.0%)</td>
<td></td>
</tr>
<tr>
<td>Not tested</td>
<td>14 (12.3%)</td>
<td>4 (3.3%)</td>
<td>3 (1.3%)</td>
<td></td>
</tr>
<tr>
<td>Mean BMI</td>
<td>27.9±6.6</td>
<td>27.1±5.3</td>
<td>26.9±5.7</td>
<td>0.31</td>
</tr>
<tr>
<td>Smoking</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>20 (16.8%)</td>
<td>40 (33.3%)</td>
<td>54 (24.2%)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>99 (83.2%)</td>
<td>80 (66.7%)</td>
<td>91 (56.6%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>...</td>
<td>...</td>
<td>13 (8.2%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (6.1%)</td>
<td>5 (4.2%)</td>
<td>24 (10.7%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>107 (93.9%)</td>
<td>115 (95.8%)</td>
<td>200 (88.9%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>0</td>
<td>1 (0.4%)</td>
<td></td>
</tr>
<tr>
<td>Median, creatinine (mg/mL)</td>
<td>0.84 (0.22)</td>
<td>0.90 (0.30)</td>
<td>0.80 (0.30)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Mean, eGFR (mL/min per 1.73 m²)</td>
<td>106.3±21.7</td>
<td>101.9±25.2</td>
<td>102.1±24.6</td>
<td>0.28</td>
</tr>
</tbody>
</table>

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.
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/m²; 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 m²; 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 and more recently in a contemporary Northern European cohort by Fransen van de Putte et al. 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

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

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

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

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.
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 al19 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 al20 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)

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 5 y</td>
<td></td>
<td>1.48 (1.35;1.62); &lt;0.0001</td>
<td>1.36 (1.201.53); &lt;0.0001</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td></td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td>0.86 (0.43;1.75); 0.68</td>
<td>0.52 (0.24;1.15); 0.11</td>
</tr>
<tr>
<td>Hispanic</td>
<td></td>
<td>0.91 (0.50;1.64); 0.75</td>
<td>0.63 (0.32;1.22); 0.17</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>1.22 (0.61;2.41); 0.58</td>
<td>1.09(0.53;2.23); 0.82</td>
</tr>
<tr>
<td>Center</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAOH</td>
<td></td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>UCSD</td>
<td></td>
<td>0.89 (0.52;1.51); 0.66</td>
<td>0.88 (0.49;1.57); 0.66</td>
</tr>
<tr>
<td>TU</td>
<td></td>
<td>1.18 (0.67;2.09); 0.56</td>
<td>1.26 (0.66;2.38); 0.48</td>
</tr>
<tr>
<td>BMI, per 5 kg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever smoker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR, per mL/min per 1.73 m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemophilia type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>B</td>
<td>1.87 (1.17;2.98); 0.009</td>
<td>1.36 (0.79;2.32); 0.27</td>
<td>1.63 (0.90;2.94); 0.11</td>
</tr>
<tr>
<td>Severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td></td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Moderate/severe</td>
<td>0.87 (0.57;1.32); 0.51</td>
<td>1.30 (0.76;2.18); 0.32</td>
<td>1.51 (0.86;2.67); 0.15</td>
</tr>
</tbody>
</table>

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 catego-
rized 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 gen-
eral, 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 exer-
cise 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 fast-
ing 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 eradi-
cated 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 mea-
surements 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,
obsesity, renal function, or smoking.30–33 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 acti-
vated thrombin activatable fibrinolysis inhibitor may affect BP
regulation.35–37 Although less likely because of the >1000 differ-
ent 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 ICH13 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 repre-
senting general hemophilia care patterns in the United States. As
evidenced at the UCSD Hemophilia Treatment Center, health-
care 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.

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Disclosures

None.

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Prevalence and risk factors of cardiovascular disease (CVD) events
among patients with haemophilia: experience of a single haemophilia
Wilber N. Mortality among males with hemophilia: relations with source

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
Annette von Drygalski, Nicholas A. Kolaitis, Ricki Bettencourt, Jaclyn Bergstrom, R. Kruse-Jarres, Doris V. Quon, Christina Wassel, Ming C. Li, Jill Waalen, Darlene J. Elias, Laurent O. Mosnier and Matthew Allison

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http://hyper.ahajournals.org/content/suppl/2013/04/30/HYPERTENSIONAHA.113.01174.DC1

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Prevalence and Risk Factors for Hypertension in Hemophilia

Online Supplemental Data Table

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⁴ Tulane University, School of Medicine, Section of Hematology/Oncology, New Orleans, USA
⁵ Hemophilia Treatment Center, Orthopaedic Hospital, Los Angeles, CA

Short title: von Drygalski- Hypertension of Hemophilia

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Office (619) 471-0335
Fax (619) 471 -0338
avondrygalski@ucsd.edu
<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>No HTN (n=233)</th>
<th>HTN (n=225)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>34.4 ± 10.8</td>
<td>48.3 ± 15.3</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Ethnicity, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>114 (48.9%)</td>
<td>128 (56.9%)</td>
<td>.10</td>
</tr>
<tr>
<td>Black</td>
<td>26 (11.2%)</td>
<td>24 (10.7%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>67 (28.8%)</td>
<td>43 (19.1%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>26 (11.2%)</td>
<td>30 (13.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>26.2 ± 5.5</td>
<td>28.2 ± 6.0</td>
<td>.0005</td>
</tr>
<tr>
<td><strong>Ever Smoker, n (%)</strong></td>
<td>62 (26.6%)</td>
<td>75 (33.3%)</td>
<td>.06</td>
</tr>
<tr>
<td><strong>Diabetes, n (%)</strong></td>
<td>4 (1.7%)</td>
<td>31 (13.8%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Creatinine</strong></td>
<td>0.83 (0.26)</td>
<td>0.90 (0.20)</td>
<td>.002</td>
</tr>
<tr>
<td><strong>eGFR, mL/min/1.73m²</strong></td>
<td>112.0 ± 18.2</td>
<td>94.4 ± 25.9</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>HIV, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Tested</td>
<td>18 (7.7%)</td>
<td>14 (6.2%)</td>
<td>.20</td>
</tr>
<tr>
<td>Positive</td>
<td>45 (19.3%)</td>
<td>59 (26.2%)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>170 (73.0%)</td>
<td>152 (67.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>HepC positive, n (%)</strong></td>
<td>11 (4.7%)</td>
<td>10 (4.4%)</td>
<td>.006</td>
</tr>
<tr>
<td>Not Tested</td>
<td>137 (58.8%)</td>
<td>163 (72.4%)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>85 (36.5%)</td>
<td>52 (23.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Hemophilia Severity, n (%)</strong></td>
<td>64 (27.5%)</td>
<td>70 (31.1%)</td>
<td>.0004</td>
</tr>
<tr>
<td>Mild</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>23 (9.9%)</td>
<td>49 (21.8%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>146 (62.7%)</td>
<td>106 (42.1%)</td>
<td></td>
</tr>
</tbody>
</table>

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