

University of Groningen

Carotid plaque composition in persons with hemophilia

Hop, Hilde; Potze, Jan-Hendrik; van den Berg-Faaij, Sandra; Borra, Ronald J. H.; Zheng, Kang H.; Nederveen, Aart J.; Meijer, Karina; Kamphuisen, Pieter Willem

Published in:
Thrombosis Research

DOI:
[10.1016/j.thromres.2020.10.036](https://doi.org/10.1016/j.thromres.2020.10.036)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Hop, H., Potze, J.-H., van den Berg-Faaij, S., Borra, R. J. H., Zheng, K. H., Nederveen, A. J., Meijer, K., & Kamphuisen, P. W. (2021). Carotid plaque composition in persons with hemophilia: An explorative study with multi-contrast MRI. *Thrombosis Research*, 197, 138-140.
<https://doi.org/10.1016/j.thromres.2020.10.036>

Copyright

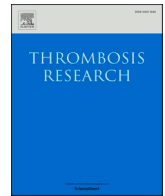
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.



Letter to the Editors-in-Chief

Carotid plaque composition in persons with hemophilia: An explorative study with multi-contrast MRI

Dear Editors,

Persons with hemophilia (PWH), who have a congenital deficiency of clotting factor VIII or IX, are thought to be protected from acute cardiovascular disease (CVD) [1]. This protection is hypothesized to be conferred by decreased thrombin generation which slows the formation of an arterial thrombus. In recent years, it has become clear that acute CVD does occur in PWH [2]. This raises the question whether the potentially protective effect of hypocoagulability is offset by other, adverse, effects on the process that leads to arterial disease.

Atherosclerotic plaque rupture or erosion is a key feature in the occurrence of an acute cardiovascular event. Imaging studies have established that plaque burden and high-risk compositional features, such as intraplaque hemorrhage (IPH), a large lipid-rich necrotic core (LR/NC) and a thin or ruptured fibrous cap, are strongly associated with CVD event risk [3]. Previous studies among relatively young PWH and controls of similar age showed a comparable degree of atherosclerosis, as measured with coronary artery calcium scoring and carotid artery ultrasound [4,5]. However, plaque compositional features have not been studied in hemophilia before. Therefore, in an explorative, cross-sectional study we evaluated whether plaque composition in PWH with atherosclerosis differs from that in controls without bleeding disorder. Presence of IPH and LR/NC in the carotid arteries was assessed using 3-Tesla magnetic resonance imaging (MRI). Furthermore, the fibrous cap was assessed in those subjects with a LR/NC.

We included PWH and sex- and age-matched controls ≥ 50 years, who had no history of symptomatic carotid atherosclerotic disease, no claustrophobia or other MRI-related contra-indications and who were not using anticoagulants (vitamin K antagonists and direct oral anticoagulants, use of antiplatelet drugs was permitted). On group level PWH and controls were matched for presence of cardiovascular disease, diabetes mellitus and use of antihypertensive medication.

Clinical data were obtained through a standardized questionnaire (cardiovascular risk factors and medication), measurement (blood pressure, BMI, lipid profile, HbA1c) and review of medical records (type and severity of hemophilia). All participants were imaged with a 3 Tesla MRI scanner (Magnetom Skyra, Siemens, Erlangen, Germany) and a dedicated surface coil (Bilateral Four Channel Phased Array Carotid Coil, Machnet BV, Roden, The Netherlands). After identification of the carotid bifurcations with a 3D-magnetization-prepared rapid gradient-echo (MP-RAGE) sequence, four sequences in the axial plan were obtained: a T1-weighted spin echo sequence, a T2-weighted turbo spin echo sequence, a proton density (PD) weighted spin echo sequence and a contrast-enhanced (CE) T1-weighted spin echo sequence. Furthermore, a 3D contrast-enhanced magnetic resonance angiography (CE-MRA) was obtained after administration of gadoterate meglumine (Dotarem, Guerbet, Roissy CdG Cedex, France). Scan parameters were as follows:

for T1-weighted sequences the repetition time (TR), echo time (TE) and flip angle (FA) were 650 ms, 16 ms and 70° respectively. For the T2-weighted sequence TR was 4000 ms, TE 82 ms and FA 175° . For the PD-weighted sequence TR was 2000 ms, TE 11 ms and FA 120° . The field-of-view was 200×150 mm for all sequences except for CE-MRA, which was 330×248 mm. The matrix size was 384×326 mm. The slice thickness was 2 mm in all weightings with the exception of CE-MRA, which was 0.9 mm. The reconstructed voxel size was $0.3 \times 0.3 \times 2$ mm in all sequences, but $0.9 \times 0.9 \times 0.9$ in CE-MRA.

In order to assess the carotid artery wall thickness, the inner and outer contours of the vessel wall were manually delineated on the PD-weighted sequences by two independent readers (SBF and HH) using vessel wall analysis software (VesselMass, Leiden University Medical Center, Leiden, The Netherlands). Both readers were blinded for group, scan date and demographic data. Participants with a low image quality, assessed according to a previously described method, were excluded [6]. The first slice showing the internal and external carotid artery separately

Table 1
Baseline characteristics.

	PWH (n = 20)	Controls (n = 20)	P-value
Median age (IQR)	61 (55–70)	62 (57–69)	–
Hemophilia A/B (%)	17 (85)/3 (15)	–	–
Severity of hemophilia			
Severe (%)	5 (25)	–	–
Moderate (%)	3 (15)	–	–
Mild (%)	12 (60)	–	–
CVD (%)	1	1	–
Diabetes mellitus (%)	3 (15)	3 (15)	–
Smoking status			
Current smoker (%)	5 (25)	4 (20)	1.000
Former smoker (%)	11 (55)	8 (40)	0.375
Use of anti-hypertensive drugs (%)	6 (30)	5 (25)	–
Use of lipid lowering drugs (%)	3 (15)	6 (30)	0.375
Median BMI, kg/m ² (IQR)	26 (25–28)	27 (24–29)	0.881
BMI ≥ 25 kg/m ² (%)	15 (52)	14 (48)	1.000
Median systolic blood pressure, mm Hg (IQR)	148 (137–162)	149 (138–154)	0.695
Median diastolic blood pressure, mm Hg (IQR)	90 (77–96)	85 (77–93)	0.968
Total cholesterol, mmol/L (IQR)	5.1 (3.9–5.5)	4.8 (4.2–5.2)	0.896
LDL-cholesterol, mmol/L (IQR)	3.5 (2.4–4)	3.2 (2.5–3.8)	0.627
HDL-cholesterol, mmol/L (IQR)	1.2 (1.1–1.4)	1.4 (1.2–1.8)	0.058
HbA1c, mmol/mol (IQR)	40 (35–42)	34 (34–41)	0.248

Data is presented as numbers unless otherwise specified.

Abbreviations: PWH, persons with hemophilia; SD, standard deviation; IQR, interquartile range; CVD, cardiovascular disease; BMI, body-mass index; LDL, low-density lipoprotein; HDL, low-density lipoprotein.

<https://doi.org/10.1016/j.thromres.2020.10.036>

Received 17 June 2020; Received in revised form 11 October 2020; Accepted 31 October 2020

Available online 6 November 2020

0049-3848/© 2020 Elsevier Ltd. All rights reserved.

was used as reference. From here, two slice above and six slices below the reference were assessed. The software automatically calculated the mean and maximal vessel wall thickness for the left and right carotid artery separately. In 14 out of 80 arteries the presence of unsuppressed blood in the lumen complicated vessel wall delineation. In those cases the readers jointly evaluated the PD- and T1-weighted sequences and MRA images using RadiAnt Dicom Viewer (Medixant, Poznan, Poland). In six of them consensus could be reached and in eight cases a third independent assessor (AJN) decided whether wall thickening was consistent with atherosclerosis. After this evaluation, the assessors independently redrew the vessel contours if necessary. The mean of both readers was used in the analysis.

The composition of all atherosclerotic plaques, defined as a maximal vessel wall thickness of ≥ 2 mm, was evaluated by comparing all obtained MR contrast weightings in RadiAnt Dicom Viewer [7]. Plaque features were determined according to previous studies [6,8]. One reader (HH) first evaluated the images. In case of a possible IPH or LR/NC an independent second reader (KHZ or AJN) was asked to interpret the images.

Continuous variables were presented as mean \pm SD or median values with the 25th and 75th percentile, categorical variables as counts and percentages.

A total of 48 potentially eligible PWH were invited, of which 25 were willing to participate. Five of them were excluded because of a cardiac pacemaker ($n = 1$) or claustrophobia ($n = 4$), resulting in 20 included PWH. Characteristics of all included participants are listed in Table 1. All PWH with severe disease were on prophylactic treatment. None of the PWH had a chronic hepatitis B or C infection. Of the 23 potentially eligible controls, three were excluded because of low MRI scan quality, resulting in 20 controls. All included participants were Caucasian.

The overall mean and maximum vessel wall thickness was comparable between PWH and controls (mean 1.07 mm [0.96–1.21] vs. 1.04 mm [0.97–1.15], $p = 0.502$; maximum 1.58 mm [1.36–2.29] vs. 1.52 mm [1.31–1.81], $p = 0.188$). Atherosclerotic plaques were found in 14 participants; 8 (40%) PWH and 6 (30%) controls ($p = 0.774$). Three PWH and one control had bilateral carotid plaques, resulting in a total of eleven plaques in PWH and seven plaques in controls. IPH was present in none of the atherosclerotic plaques. LR/NC was found in three PWH

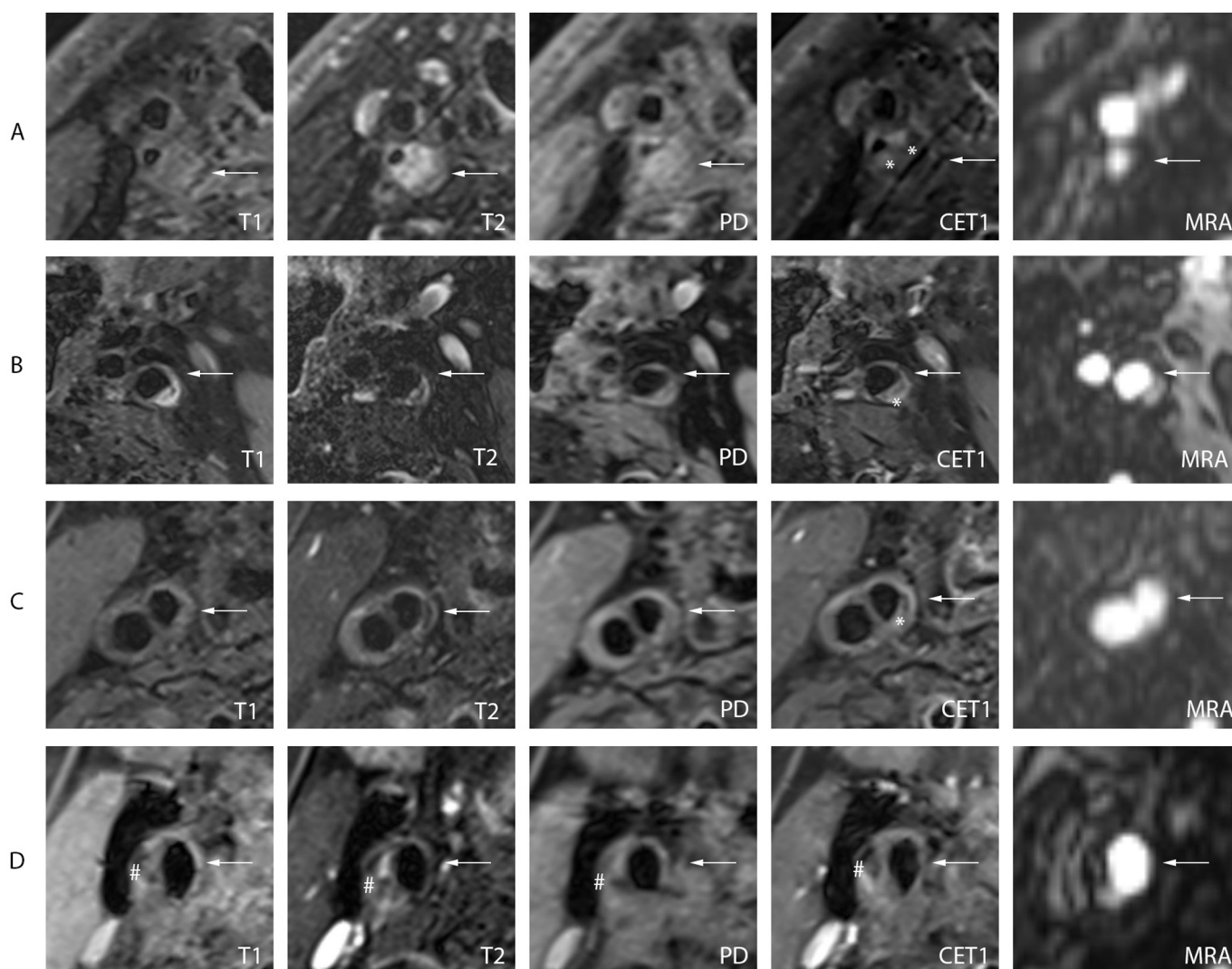


Fig. 1. The carotid artery bifurcation of a person with hemophilia (A, B, C) and a control without bleeding disorder (D). (A) Severe stenosis ($\geq 70\%$) of the right internal carotid artery (arrow). The plaque shows hypointense areas on contrast enhanced T1- weighted images (*), while these areas appear isointense on T1- and T2- weighted images and iso- to hyperintense on PD-weighted images. This points to the presence of a LR/NC in the plaque. The fibrous cap cannot be reliably assessed due to an artifact. (B) Small plaque (arrow) with a LR/NC (*) and a thick fibrous cap in the left external carotid artery. (C) Vessel wall thickening in right carotid artery bifurcation. A small plaque (arrow) with a LR/NC (*) and a thick fibrous cap in the external carotid artery can be seen. (D) A mixed atherosclerotic plaque in the right carotid artery bifurcation. The plaques shows a hypointense area (#) on all weightings, suggesting the presence of a calcified plaque. Abbreviations; LR/NC, lipid-rich necrotic core.

(one with severe hemophilia B, one with moderate hemophilia A and one with mild hemophilia A), and in none of the controls (Fig. 1). Two out of three PWH with a LR/NC had a thick fibrous cap, the other fibrous cap could not be reliably assessed due to an artifact.

PWH with atherosclerotic plaques (n = 8) were older than PWH without plaques (n = 12) (69[59–72] vs. 59[52–63], p = 0.047) and more frequently active smokers (4[50%] vs. 1 [8%], p = 0.035). Furthermore, PWH with plaques more frequently used antihypertensive drugs, although not significantly (4[50%] vs. 2[17%], p = 0.161). No differences were found with respect to other classical CVD risk factors or type and severity of hemophilia.

The finding of a LR/NC in three older PWH with cardiovascular risk factors, while none of the controls had a LR/NC, confirms that PWH are able to develop advanced atherosclerosis. Previously, a temporary hypocoagulable state because of anticoagulant treatment with vitamin K antagonists has been associated with an increased risk of IPH [9]. Therefore, one can speculate that in PWH, who have a lifelong hypocoagulable state, IPH occurs earlier and to a larger extent. However, we did not find any IPH in our study population. Even in the three PWH with a LR/NC, as sign of plaque progression, no IPH was found. A possible explanation is that anticoagulation treatment with vitamin K antagonists has an effect on coagulation proteins expressed by the atherosclerotic plaque itself, such as VII produced by local vascular smooth muscle cells, while changes in systemic coagulation factors VIII and IX might not have such an effect [10].

The fact that we found a LR/NC in PWH, but not in controls implicates that some PWH in our study had a more advanced stage of atherosclerosis. This might be related to hemophilia, but might also be explained by difference in risk factors between both groups. Although the groups were matched for the most important cardiovascular risk factors, statin use was lower in PWH and the lipid profile worse, which hampers the interpretation of the data on LR/NC.

Another limitation that should be considered is the inclusion of persons with mild as well as severe hemophilia. When hemophilia is related to plaque composition the strongest association would be expected in persons with severe hemophilia and proven atherosclerotic plaques. However, inclusion of only PWH with severe disease would have been difficult due to the limited number of eligible participants in our center. Moreover, our results do not support any relationship between atherosclerosis development and severity of hemophilia.

Taking into account the small sample size of the study, we conclude that IPH or fibrous cap rupture is not an important feature of atherosclerotic plaques in PWH. Whether the increased prevalence of LR/NC is related to hemophilia needs further investigation. We have confirmed that, despite a permanent hypocoagulable state, PWH are able to develop advanced atherosclerosis of the carotid artery.

Financial support

This study was supported by an ASPIRE Hemophilia Research Award from Pfizer. Pfizer was not involved in the design of the study or collection, management, analysis and interpretation of the data, writing of the report, or the decision to submit the paper for publication.

Declaration of competing interest

The study was supported by an ASPIRE Hemophilia Research Award

from Pfizer.

Pfizer was not included in study design, data collection or analysis, report writing or submission.

K. Meijer reports grants/travel support/and speaker fees from Bayer, Sanguin, Pfizer, Boehringer BMS and Aspen, all outside the submitted work. K. Meijer also reports consulting fees from UniQure.

The other authors report no conflicts.

References

- [1] N. Sousos, E. Gavrilaki, S. Vakalopoulou, V. Garipidou, Understanding cardiovascular risk in hemophilia: a step towards prevention and management, *Thromb. Res.* 140 (2016) 14–21.
- [2] S. Lovdahl, K.M. Henriksson, F. Baghaei, M. Holmstrom, E. Berntorp, J. Astermark, Hypertension and cardiovascular diseases in swedish persons with haemophilia - a longitudinal registry study, *Thromb. Res.* 181 (2019) 106–111.
- [3] A.E. Zavodni, B.A. Wasserman, R.L. McClelland, et al., Carotid artery plaque morphology and composition in relation to incident cardiovascular events: the multi-ethnic study of atherosclerosis (MESA), *Radiology.* 271 (2) (2014) 381–389.
- [4] M. Zwiers, J.D. Lefrandt, D.J. Mulder, et al., Coronary artery calcification score and carotid intima-media thickness in patients with hemophilia, *J. Thromb. Haemost.* 10 (1) (2012) 23–29.
- [5] S. Biere-Rafi, A. Tuinenburg, B.W. Haak, et al., Factor VIII deficiency does not protect against atherosclerosis, *J. Thromb. Haemost.* 10 (1) (2012) 30–37.
- [6] C. Yuan, L.M. Mitsumori, M.S. Ferguson, et al., In vivo accuracy of multispectral magnetic resonance imaging for identifying lipid-rich necrotic cores and intraplaque hemorrhage in advanced human carotid plaques, *Circulation.* 104 (17) (2001) 2051–2056.
- [7] M.T. Truijman, M.E. Kooi, A.C. van Dijk, et al., Plaque at RISK (PARISK): prospective multicenter study to improve diagnosis of high-risk carotid plaques, *Int. J. Stroke* 9 (6) (2014) 747–754.
- [8] H. Ota, W. Yu, H.R. Underhill, et al., Hemorrhage and large lipid-rich necrotic cores are independently associated with thin or ruptured fibrous caps: an in vivo 3T MRI study, *Arterioscler. Thromb. Vasc. Biol.* 29 (10) (2009) 1696–1701.
- [9] B. Mujaj, D. Bos, T. Muka, et al., Antithrombotic treatment is associated with intraplaque haemorrhage in the atherosclerotic carotid artery: a cross-sectional analysis of the Rotterdam study, *Eur. Heart J.* 39 (36) (2018) 3369–3376.
- [10] G.A.J.C. Crombag, H.M. Spronk, P. Nelemans, et al., No association between thrombin generation and intra-plaque haemorrhage in symptomatic carotid atherosclerotic plaques: the plaque at RISK (PARISK) study, *Thromb. Haemost.* 118 (8) (2018) 1461–1469.

Hilde Hop^{a,*}, Jan-Hendrik Potze^b, Sandra van den Berg-Faaij^c, Ronald J. H. Borra^b, Kang H. Zheng^d, Aart J. Nederveen^c, Karina Meijer^e, Pieter Willem Kamphuisen^{a,f}

^a Department of Internal Medicine, University Medical Center Groningen, University of Groningen, the Netherlands

^b Medical Imaging Center, University Medical Center Groningen, University of Groningen, the Netherlands

^c Department of Radiology and Nuclear Medicine, Amsterdam University Medical Center, location AMC, the Netherlands

^d Department of Vascular Medicine, Amsterdam University Medical Center, location AMC, the Netherlands

^e Department of Hematology, University Medical Center Groningen, University of Groningen, the Netherlands

^f Department of Internal Medicine, Tergooi Hospital, location Hilversum, the Netherlands

* Corresponding author at: University Medical Center Groningen, Department of Internal Medicine, Division of Vascular Medicine, Hanzeplein 1, 9713 GZ Groningen, the Netherlands.

E-mail address: h.hop@umcg.nl (H. Hop).