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SHORT COMMUNICATION

Pulse wave velocity measurement as a marker of arterial stiffness in pediatric inflammatory bowel disease: a pilot study

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Abstract In adults with inflammatory bowel disease (IBD), the incidence of cardiovascular events is increased, leading to long-term morbidity. Arterial stiffness (AS) measured by pulse wave velocity (PWV) is a validated early precursor of cardiovascular disease (CVD), and measurement of PWV was shown to be a feasible test in children. The aim of this study was to assess AS in children with IBD. In this prospective study, we determined PWV between the carotid and femoral artery (PWV_{cf}) in 25 children and adolescents with IBD (11 females, median age 14.1 years, median disease duration 2.8 years). The majority (68%) of the subjects were in clinical remission, and 48% received anti-tumor necrosis factor alpha (TNFα) treatment. AS was not increased in this cohort of children and adolescents with IBD, who did not have signs of cardiovascular disease, such as arterial hypertension.

Conclusion: PWV seems to be normal in children with IBD in remission or with mild disease activity. Larger studies should assess its potential role as a valid and non-invasive follow-up marker in children with IBD, to avoid cardiovascular complications.

What is Known:

- *Inflammatory bowel disease (IBD) is a risk factor of cardiovascular disease (CVD).*
- *Pulse wave velocity (PWV) measurement is the current gold standard to assess arterial stiffness (AS), which is an early predictor of CVD.*

What is New:

- *This is the first study using PWV measurements to determine AS in children with IBD.*
- *In children with IBD in remission or only mild disease activity AS is not increased.*

Keywords Arterial stiffness · Cardiovascular disease · Inflammation · IBD · Pulse wave velocity · PWV

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Abbreviations

AS	Arterial stiffness
CVD	Cardio vascular disease
IBD	Inflammatory bowel disease
PWV_{cf}	Carotid–femoral pulse wave velocity
TNFα	Tumor necrosis factor alpha

Introduction

Inflammatory bowel disease (IBD) is characterized by chronic intestinal inflammation and can be sub-classified into Crohn's disease (CD) and Ulcerative Colitis (UC) [1]. In adults with IBD, cardiovascular complications such as thrombotic events and early atherosclerosis are well documented and are increasingly reported in children with IBD [2, 3]. Despite a lower incidence of classical risk factors such as dyslipidemia, arterial hypertension, or diabetes mellitus [4], atypical cardiovascular risk factors such as hyperhomocysteinemia [5] and endothelial dysfunction [6] may explain the increased risk of cardiovascular disease (CVD) in patients with IBD. Pulse wave velocity (PWV) is the current gold standard to determine arterial stiffness (AS), an early sign of CVD, in children [7]. In adults, studies have shown increased AS in patients with IBD but no data on AS exist for children with IBD [5, 8].

As such, we hypothesized that children with IBD have increased AS. The aim of this study was to measure the carotid femoral PWV (PWV_{cf}) in a cohort of children and adolescents with IBD.

Patients and methods

Study population

This cross-sectional, prospective pilot cohort study was performed at the Children's University Hospital, Berne, from February to June 2013. The patients eligible for recruitment to the study were children and adolescents younger than 18 years with a diagnosis of IBD according to the Porto criteria and followed in the pediatric gastroenterology clinic at the Children's University hospital in Bern. Exclusion criteria were the presence of any abnormalities of the cardiovascular system (e.g., congenital heart diseases or known coagulation disorder) and/or limbs (the latter would make the measurement of arterial stiffness impossible).

Written informed consent was obtained prior to study enrolment. The study was approved by the local research ethics committee.

Clinical and biochemical assessment

As part of routine clinical care, anthropometric data including height, weight, body mass index (BMI), and puberty stage (Tanner stages) were recorded. Standard laboratory blood tests such as C-reactive protein (CRP, norm <3 mg/dl), erythrocyte sedimentation rate (ESR), glucose, hemoglobin, white blood cell count and albumin, and stool calprotectin (norm <200 mg/kg), a fecal marker of disease activity, were obtained. Classic cardiovascular risk factors such as diabetes mellitus, arterial hypertension, obesity, smoking, or corticosteroid therapy were documented. Disease phenotypic data were recorded, including disease duration and current medication history. Clinical disease activity was calculated using established indices, the pediatric ulcerative colitis activity index (PUCAI) for children with UC, and the pediatric Crohn's disease activity index (PCDAI) for children with Crohn's disease. (http://www.naspghan.org/files/documents/pdfs/cme/podcasts/MonitoringDiseaseActivity_PediatricIBDPatients.pdf).

Pulse wave velocity measurements

After a 10 min episode of horizontal resting, arterial blood pressure was measured on the subjects' right arm using an age appropriate blood pressure cuff. PWV_{cf} between the carotid and femoral artery was measured by means of the validated Vicorder™ device (Skidmore Medical Limited, Bristol, UK). This was performed by measuring the distance between the midpoints of two oscillometric cuffs, (i) placed at the collar (carotid artery) and (ii) at the proximal right femur (femoral artery). To account for the difference between the tape-measured distance between both cuffs and the reference distance, a correction factor of 0.8 was used. Subsequently, the automatically recorded transit time, reflecting the time lag between pulse wave registration at the carotid and femoral cuffs, was divided by distance (m). Data were obtained using the same device and measurement protocol as was used to derive pediatric age, gender, and height-related reference values for PWV_{cf}, which were modeled using the modified LMS method of Cole and Green [9, 10]. The mean PWV_{cf} of three measurements was taken as the primary outcome. Data were expressed in m/s and z scores, according to Fischer and colleagues [10].

Statistical analysis

Graph Pad Prism (GraphPad Software, San Diego, California, USA) was used for statistical analysis. Descriptive data are expressed as median with interquartile range (IQR). Relationships among variables were assessed by using a best-fit linear regression analysis. Uni- and multivariate correlation was calculated. Mann–Whitney U test or student t test were used to compare groups. Significance was assigned at $p < 0.05$.

Results

In total, 25 children with IBD (10 with UC and 15 with CD) were approached and found to be eligible for enrollment in the study.

All children had normal PWV_{cf} (<95 percentile). PWV_{cf} median (interquartile range) was 4.4 m/s (4.0–5.2), reflecting a median z score of −0.1 (−1.0–0.5). There was no difference of the PWV_{cf} in children with UC or CD; ($p = 0.4$; Table 1). A linear correlation ($r^2 = 0.4$) of PWV_{cf} with age was observed, and children had normal systolic and diastolic blood pressure for gender, height, and age (Table 1).

The majority (n = 17; 68%) of subjects were in clinical remission indicated by PUCAI/PCDAI scores <10. Two of the eight children with active clinical disease (PUCAI/PCDAI scores >10) had elevated levels of CRP (4 and 14 mg/L) and in four (50%) fecal calprotectin was abnormal.

No patient was undergoing treatment with corticosteroids at time of PWV measurement. Infliximab, a monoclonal TNFα antibody was given to 12 (48%) subjects of which 9 (75%) were in clinical remission. The remaining children were treated with Methotrexate (n = 2), Azathioprine (n = 9), and/or Mesalazine (n = 12), of which 61% were in remission. No cardiovascular risk factors (obesity, arterial hypertension, diabetes mellitus, or smoking) were present. In univariate and multivariate correlation analysis, PWV_{cf} was not associated with fecal and systemic markers of inflammation (Calprotectin, CRP, ESR, Albumin), disease activity scores (PUCAI for UC and PCDAI for CD), blood pressure, or disease duration. The cohort was too small to compare for differences of treatment regimes.

Discussion

This is the first study assessing early CVD risk factors by means of AS, measured by PWV_{cf}, in children with IBD. In this cohort of children with mostly quiescent IBD, AS was normal regardless of the underlying diagnosis (UC vs. CD), and no correlation with clinical disease activity scores was seen.

We speculate that this result might be related to the overall high rate of clinical remission (68%), and otherwise mild disease activity in our cohort. A group from Italy recently showed that children with IBD had early signs of atherosclerosis measured by the intima media thickness of the carotid and brachial arteries, as well as the abdominal aorta [11, 12]. Nevertheless, a different method to assess CVD risk was applied in this group, and remission rate was significant lower (36% of children with CD and 28% with UC compared to 68% in our cohort). These differences might explain the dissimilar results and support our theory that clinical remission is associated with normal AS [11].

The relatively high rate of children in remission in our study is likely a result of the use of anti-inflammatory treatments with anti-TNFα agents (48%) or immune modulators

Table 1 Demographic data and measurements of children with inflammatory bowel disease

	All	Ulcerative colitis	Crohn's disease	
n	25	10	15	
Female (%)	11(44)	5 (50)	6 (40)	ns
Disease duration, years	2.8 [1.4–5.4]	1.8 [1–4.8]	3.8 [1.9–7]	ns
Age, years	14.1 [10.9–16.1]	10.3 [7.9–11.8]	14.4 [11.7–16.4]	ns
Height, cm	153.0 [142.1–171.0]	149.5 [137.4–162.0]	157.0 [142.1–172.9]	ns
Height, z scores	−0.3 [−1.3–0.5]	−0.4 [−1.9–0.4]	−0.1 [−1.2–0.6]	ns
Weight, kg	43.0 [35.5–54.5]	42.1 [32.8–47.4]	47.4 [37.9–58.0]	ns
Weight, z scores	−0.6 [−1.1–0.4]	−0.3 [−1.1–0.1]	−0.6 [−1.2–0.5]	ns
BMI, kg/m^2	18.4 [17.2–19.7]	18.4 [16.1–19.8]	18.4 [17.2–19.8]	ns
BMI z scores	−0.4 [−0.8–0.2]	−0.4 [−0.5–0.5]	−0.3 [−1.0–0.2]	ns
Systolic BP z scores	−0.7 [−0.9–0.2]	−0.7 [−0.9–0.1]	−0.7 [−1.2–0.4]	ns
Diastolic BP z scores	−0.2 [−0.6–0.3]	−0.4 [−0.6–0.2]	0.1 [−0.3–0.7]	ns
PWV, m/s	4.4 [4.0–5.2]	4.2 [3.5–4.8]	4.6 [4.0–5.2]	ns
PWV, z scores	−0.1 [−1.0–0.5]	−0.5 [−1.3–0.2]	0.1 [−0.9–0.5]	ns
PUCAI / PCDAI >10 (%)	8 (32)	6 (60)	2 (13)	0.03*
Calprotectin, mg/kg	221 [74–573]	256 [68–721]	221 [87–527]	ns
C-reactive protein, mg/l	0 [0–5]	0 [0–2.5]	0 [0–6]	ns

If not otherwise stated results are expressed in median [IQR]

BP blood pressure, *PWV* pulse wave velocity, *PUCAI* pediatric ulcerative colitis activity index, *PCDAI* pediatric Crohn's disease activity index, *ns* not significant

*Significant

(39%). Data in adults are suggestive that these therapies, especially anti-TNFα agents, positively impact AS in patients with IBD and other systemic inflammatory diseases such as rheumatoid arthritis, through improvement of endothelial function [5, 8].

In addition, there was no correlation between PWV and disease duration in our cohort, which is different to the experience in adults with IBD [5, 8]. Due to a relatively short overall disease duration in our cohort (median 2.8 years) compared with 5.9 years (UC) and 7.0 years (CD) in adults, early changes of the vascular endothelium might not have yet occurred [8].We have to acknowledge several limitations of our study. First, it is a cross-sectional study of a relatively small and heterogeneous cohort, limiting a causal interpretation of the results. In addition, no comparison group was available; however, established age- and gender-related reference values exist and were used for result interpretation. Finally, given that the majority of patients with active clinical disease (6/8) had a normal CRP and 50% had a normal fecal calprotectin, the rate of children in remission is likely to have been even higher in our cohort, limiting our ability to determine the differences in AS in children with active inflammatory disease.

In conclusion, AS measured by PWV_{cf} seems to be normal in children with quiescent IBD. Larger longitudinal studies are needed to elucidate how this finding translates into long-term outcomes of CVD in patients with IBD, and if PWV_{cf} measurements might have a role as a non-invasive follow-up marker to detect and potentially prevent extra-intestinal complications.

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Authors' contributions Eberhard Lurz was responsible for data acquisition, for drafting the manuscript, revising it critically for important intellectual content and he was responsible for the final approval of the manuscript to be published.

Eliane Aeschbacher was responsible for conception and design, data acquisition, analysis and interpretation of data. She was responsible for the final approval of the manuscript to be published.

Nicholas Carman revised it critically for important intellectual content, he played an important role in the revision of the manuscript and he was responsible for the final approval of the manuscript to be published.

Susanne Schibli was responsible for conception and design, she revised it critically for important intellectual content and she was responsible for the final approval of the manuscript to be published.

Christiane Sokollik was responsible for drafting the manuscript, revising it critically for important intellectual content and she was responsible for the final approval of the manuscript to be published.

Giacomo D. Simonetti was responsible for conception and design, analysis and interpretation of data, and drafting the manuscript. He was responsible for the final approval of the manuscript to be published.

Compliance with ethical Standads

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Ruel J, Ruane D, Mehandru S, Gower-Rousseau C, Colombel JF (2014) IBD across the age spectrum: is it the same disease? Nat Rev Gastroenterol Hepatol 11(2):88–98. doi:10.1038/nrgastro.2013.240
2. Yarur AJ, Deshpande AR, Pechman DM, Tamariz L, Abreu MT, Sussman DA (2011) Inflammatory bowel disease is associated with an increased incidence of cardiovascular events. Am J Gastroenterol 106(4):741–747. doi:10.1038/ajg.2011.63
3. Kappelman MD, Horvath-Puho E, Sandler RS, Rubin DT, Ullman TA, Pedersen L, Baron JA, Sorensen HT (2011) Thromboembolic risk among Danish children and adults with inflammatory bowel diseases: a population-based nationwide study. Gut 60(7):937–943. doi:10.1136/gut.2010.228585
4. Zanoli L, Rastelli S, Inserra G, Castellino P (2015) Arterial structure and function in inflammatory bowel disease. World J Gastroenterol 21(40):11304–11311. doi:10.3748/wjg.v21.i40.11304
5. Ozturk K, Guler AK, Cakir M, Ozen A, Demirci H, Turker T, Demirbas S, Uygun A, Gulsen M, Bagci S (2015) Pulse wave velocity, intima media thickness, and flow-mediated dilatation in patients with normotensive normoglycemic inflammatory bowel disease. Inflamm Bowel Dis 21(6):1314–1320. doi:10.1097/MIB.0000000000000355
6. Principi M, Mastrolonardo M, Scicchitano P, Gesualdo M, Sassara M, Guida P, Bucci A, Zito A, Caputo P, Albano F, Ierardi E, Di Leo A, Ciccone MM (2013) Endothelial function and cardiovascular risk in active inflammatory bowel diseases. Journal of Crohn's & colitis 7(10):e427–e433. doi:10.1016/j.crohns.2013.02.001
7. Urbina EM, Williams RV, Alpert BS, Collins RT, Daniels SR, Hayman L, Jacobson M, Mahoney L, Mietus-Snyder M, Rocchini A, Steinberger J, McCrindle B, American Heart Association Atherosclerosis H, Obesity in Youth Committee of the Council on Cardiovascular Disease in the Y (2009) Noninvasive assessment of subclinical atherosclerosis in children and adolescents: recommendations for standard assessment for clinical research: a scientific statement from the American Heart Association. Hypertension 54(5):919–950. doi:10.1161/HYPERTENSIONAHA.109.192639
8. Zanoli L, Rastelli S, Inserra G, Lentini P, Valvo E, Calcagno E, Boutouyrie P, Laurent S, Castellino P (2014) Increased arterial stiffness in inflammatory bowel diseases is dependent upon inflammation and reduced by immunomodulatory drugs. Atherosclerosis 234(2):346–351. doi:10.1016/j.atherosclerosis.2014.03.023
9. Cole TJ, Green PJ (1992) Smoothing reference centile curves: the LMS method and penalized likelihood. Stat Med 11(10):1305–1319
10. Fischer DC, Schreiver C, Heimhalt M, Noerenberg A, Haffner D (2012) Pediatric reference values of carotid-femoral pulse wave velocity determined with an oscillometric device. J Hypertens 30(11):2159–2167. doi:10.1097/HJH.0b013e3283582217

11. Aloi M, Tromba L, Rizzo V, D'Arcangelo G, Dilillo A, Blasi S, Civitelli F, Kiltzanidi D, Redler A, Viola F (2015) Aortic intima-media thickness as an early marker of atherosclerosis in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 61(1):41–46. doi:10.1097/MPG.0000000000000771

12. Aloi M, Tromba L, Di Nardo G, Dilillo A, Del Giudice E, Marocchi E, Viola F, Civitelli F, Berni A, Cucchiara S (2012) Premature subclinical atherosclerosis in pediatric inflammatory bowel disease. J Pediatr 161(4):589–594 e581. doi:10.1016/j.jpeds.2012.03.043