European Journal of Internal Medicine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Pulse wave velocity differs between ulcerative colitis and chronic kidney disease☆

Luca Zanoli [a,*], Paolo Lentini [b,**], Pierre Boutouyrie [c], Pasquale Fatuzzo [a], Antonio Granata [d], Salvatore Corrao [e], Agostino Gaudio [f], Gaetano Inserra [a], Francesco Rapisarda [a], Stefania Rastelli [a], Stephane Laurent [c], Lorenzo S. Malatino [f], Pietro Castellino [f]

[a] School of Nephrology, Department of Clinical and Experimental Medicine, University of Catania, Italy
[b] Nephrology & Dialysis, San Bassiano Hospital, Bassano del Grappa, Italy
[c] Department of Pharmacology, HEGP, AP-HP, Paris, France
[d] Nephrology and Dialysis, "St. Giovanni di Dio" Hospital, Agrigento, Italy
[e] Internal Medicine Department, National Relevance Hospital Trust ARNAS "Civico, Di Cristina, Benfratelli", Palermo, Italy
[f] Internal Medicine, Department of Clinical and Experimental Medicine, University of Catania, Italy

ARTICLE INFO

Article history:
Received 21 May 2017
Received in revised form 3 August 2017
Accepted 17 August 2017
Available online xxxx

Keywords:
Arterial stiffness
Chronic renal failure
Inflammation
Pulse wave velocity
Stiffness mismatch
Ulcerative colitis

ABSTRACT

Background: We hypothesized that a reversal of the physiological stiffness gradient, previously reported in end-stage renal disease, begins in the early stages of chronic kidney disease (CKD) and that chronic inflammation produces a different arterial phenotype in patients with ulcerative colitis (UC).
Objectives: To assess the extent of arterial stiffening in the central (carotid-femoral pulse wave velocity, cf.-PWV) and peripheral arteries (carotid-radial pulse wave velocity, cr-PWV) and to explore the determinants of the stiffness gradient in UC and in CKD.
Methods: We enrolled 45 patients with UC, 45 patients with stage 3–4 CKD and 45 matched controls.
Results: Despite the comparable cf.-PWV, the cr-PWV was higher in patients with UC than in those with CKD (median: 8.7 vs. 7.5 m/s; $p < 0.001$) and, consequently, the PWV ratio was lower (median: 0.97 vs. 1.12; $p < 0.001$). In patients with CKD a stiffness mismatch was reported starting from stage 3B. The PWV ratio was associated with age and C-reactive protein (beta: 0.08 z-score, 95%CI 0.02–0.14; $p = 0.01$) or active disease (beta: 0.43 z-score, 95%CI 0.003–0.857; $p = 0.048$) in patients with UC and with age and glomerular filtration rate (beta: −0.56 z-score, 95%CI −1.05 to −0.07; $p = 0.02$) in patients with CKD.
Conclusions: The arterial phenotype differed between UC and CKD. The reversal of the arterial stiffness gradient is evident in CKD patients starting from stage 3B but not in patients with UC and comparable cf.-PWV. In patients with UC, the stiffness of both elastic and muscular arteries is increased as a consequence of inflammation.

1. Introduction

Cardiovascular disease is the leading cause of mortality in patients with chronic kidney disease (CKD). This high rate of mortality is partially explained by an increase in aortic stiffness [1]. In young adults, the aorta is considerably more elastic than peripheral muscular arteries and provides a physiological stiffness gradient that leads to a partial reflection of the advancing pressure wave and dampens the transmission of forward traveling pressure into the microcirculation. During aging, since the stiffness of the central elastic arteries increases to a greater extent than that of peripheral muscular arteries [2], the aortic/brachial stiffness gradient is first equalized (aortic stiffness = brachial artery stiffness), and then even reverted (aortic stiffness > brachial artery stiffness). This process, called aortic-brachial stiffness mismatch [3–5], has important hemodynamic and clinical consequences since it reduces the reflection waves, increasing the reflection site distance, causes vascular damage through the enhanced transmission of forward energy waves into the microcirculation [5], contributes to the pathogenesis of white matter lesions of the brain [6] and renal dysfunction [7,8] and, at least in patients with ESRD, is strongly and independently associated with increased mortality [9].

Recently, hypothesizing that systemic inflammation was associated with functional and structural arterial stiffening in patients with

Abbreviations: AIx@75, heart-rate-adjusted central augmentation index; Anti-TNF, anti-tumor necrosis factor; cf-PWV, carotid-femoral pulse wave velocity; CKD, chronic kidney disease; cr-PWV, carotid-radial pulse wave velocity; DBP, diastolic blood pressure; eGFR, estimated GFR; IBD, inflammatory bowel disease; MBP, mean blood pressure; PP, pulse pressure; SBP, systolic blood pressure; UC, ulcerative colitis.

☆ All authors have contributed equally.

* Corresponding author at: Internal Medicine, School of Nephrology, Department of Clinical and Experimental Medicine, Policlinico Universitario, University of Catania, Via Santa Sofia 78, 95123 Catania, Italy.

** Corresponding author at: UOC Nefrologia e Dialisi, Ospedale "San Bassiano", 36061 Bassano del Grappa, (VI), Italy.

E-mail addresses: luca.zanoli@unict.it (L. Zanoli), paolo.lentini@yahoo.it (P. Lentini).

http://dx.doi.org/10.1016/j.ejim.2017.08.020
0953-6205/

inflammatory bowel disease (IBD) [10], we reported that aortic stiffness was increased [11] and that the aortic stiffening was reduced by anti-tumor necrosis factor (anti-TNF) therapy in young patients with IBD [12]. These findings were confirmed in several studies performed by independent groups, in meta-analyses performed by our group [13–15], and in a meta-analysis performed by an independent group that, methodologic issues aside [16], has also reported both increased intima-media thickness and reduced flow-mediated dilation in patients with IBD [17]. These findings, coupled to the elevated risk of coronary heart disease and cerebrovascular accident reported in patients with IBD [18], help to explain the IBD paradox: increased cardiovascular risk with a low prevalence of classic cardiovascular risk factors [19].

Both CKD and ulcerative colitis (UC) are characterized by an increase of aortic stiffness [1,9,11–15,17]. However, since the causes and the mechanisms involved in the arterial stiffening seem to be different [10,20], also the arterial phenotype, the hemodynamic and the clinical consequences could be different in UC and CKD. In this regard, in patients with UC and in those with rheumatoid arthritis, two models of chronic inflammation, it has been reported that both elastic and muscular arteries can stiffen whereas only elastic (aortic) stiffness seems to be involved in CKD [1,9,11,12,21,35]. We believe that inflammation produces a delayed stiffness mismatch during aging in UC, and that a reversal of the physiological stiffness gradient (mismatch), previously reported in chronic hemodialysis patients, begins in the early stages of CKD. Therefore, the goals of this study were 1) to assess the extent of arterial stiffening in central and peripheral arteries in patients with UC with a minimal burden of risk factors for cardiovascular disease and in those with stages 3–4 CKD with comparable aortic stiffness; 2) to explore the determinants of the stiffness gradient in patients with UC and in those with CKD.

2. Materials and methods

This was a single-center cross-sectional study conducted at the Department of Medicine of the University of Catania. A total of 135 subjects was enrolled: 45 stage 3–4 CKD were matched to both 45 patients with UC and 45 control subjects, for age, gender, heart rate, central diastolic blood pressure (DBP) and mean blood pressure (MBP). The CKD and UC subjects were also matched for carotid-femoral pulse wave velocity (cf-PWV). In order to achieve a fair match, we recruited subjects with asymptomatic hypertension and dyslipidemia as controls. Individuals with coronary heart disease, congestive heart failure, stroke, transient ischemic attack, intermittent claudication, diabetes and malignancies were excluded, as were subjects being treated for hypertension with alpha blockers, beta blockers and calcium channel blockers, and current or previous smokers (interruption of smoking < 1 year). Written informed consent was obtained from each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The study protocol had been priorly approved by the Institution's ethics committee on research on humans.

2.1. Study design

All participants were studied in a quiet room with a controlled temperature of 22 ± 1 °C after 15 min of recumbent rest. In each subject, a non-invasive hemodynamic study was performed by an expert operator blinded to clinical data and therapy. A second operator, blinded to the hemodynamic examination, collected the clinical data using a standardized questionnaire.

2.2. Hemodynamic data

The non-invasive study of hemodynamic variables was performed as follows. Brachial blood pressure measurements were taken using an oscillometric device (Dinamap ProCare 100; GE Healthcare, Milwaukee, USA).

The cf.-PWV and the carotid-radial pulse wave velocity (cr-PWV, in the right arm) were measured by a SphygmoCor device (SphygmoCor system®, AtCor Medical, Sydney, Australia) using the foot-to-foot velocity method, the intersecting tangent algorithm and the direct distance between the measurement sites [22]: PWV (m/s) = 0.8 × [direct distance (m)/Δt]. Two consecutive recordings were performed, and, if the difference between the two measurements was <0.5 m/s, the mean value was used for this analysis; otherwise, a third recording was performed, and the median value was used. In our laboratory, the intra- and intersession coefficients of variation of PWV are 3.1% and 6.8%, respectively. The PWV ratio was calculated from the ratio between cf.-PWV and cr-PWV (PWV ratio = cf.-PWV/cr-PWV).

To assess the central pulse wave profile, the radial pulse wave profile was recorded by applanation tonometry after recalibration with brachial systolic blood pressure (SBP) and DBP in the contralateral arm (SphygmoCor system®, AtCor Medical, Sydney, Australia). The central pulse wave profile was constructed using the generalized transfer function, from which the central SBP, DBP, MBP, pulse pressure (PP), augmentation pressure (reflected wave amplitude), the round trip travel time of the forward wave from the ascending aorta to the major "effective" reflection site and back (Tr) and heart-rate-adjusted central augmentation index (AIx@75) were derived as previously described and validated (Fig. 1 Panel A) [23]. The distance to the major 'effective' site of wave reflection was calculated as: distance to reflection site = cf.-PWV × Tr/2.

2.3. Biological variables

Standard laboratory were measured 1–7 days before the hemodynamic study in our centralized laboratory. The estimated GFR (eGFR) was calculated using the CKD-EPI creatinine equation [24]. The diagnosis of UC was based on established clinical, radiological, endoscopic, and histological criteria [25]. UC severity was evaluated with the Partial Mayo Score [26]; active disease was defined by the Partial Mayo Score ≥ 2.

2.4. Statistical analysis

We determined the sample size adequate to demonstrate that patients with CKD have a higher PWV ratio than patients with UC and control subjects. Full description of sample size calculation is reported in Supplementary data.

Continuous variables are presented as the median (10–90 percentile); categorical variables are presented as percentages. Clinical and hemodynamic variables were compared using Kruskal-Wallis Test for continuous variables with Dunn's test for multiple comparison and chi-squared tests for categorical variables at univariate analyses. A outlier-robust univariate linear regression analysis was used to evaluate the determinants of the PWV. The Potthoff analysis was used to compare regression lines. We performed a outlier-robust multivariate linear regression analysis of the clinical, biological and pharmacological variables that were associated with the PWV ratio in univariate linear regression analyses. *Z*-score was calculated according to the following formula: z-score = (individual value − population mean)/population standard deviation, where the mean values and standard deviation were calculated in the controls of each cohort. A two-tailed p-value < 0.05 was considered statistically significant. Statistical analyses were performed using NCSS 2007 & PASS 11 software (Gerry Hintze, Kaysville, UT, USA).

3. Results

Table 1 shows the clinical variables of the patients included in this study significantly different between groups; the remaining clinical data are reported in Supplementary Table 1. The matching process showed that the UC patients, CKD patients and control subjects were

Please cite this article as: Zanoli L, et al, Pulse wave velocity differs between ulcerative colitis and chronic kidney disease, Eur J Intern Med (2017), http://dx.doi.org/10.1016/j.ejim.2017.08.020

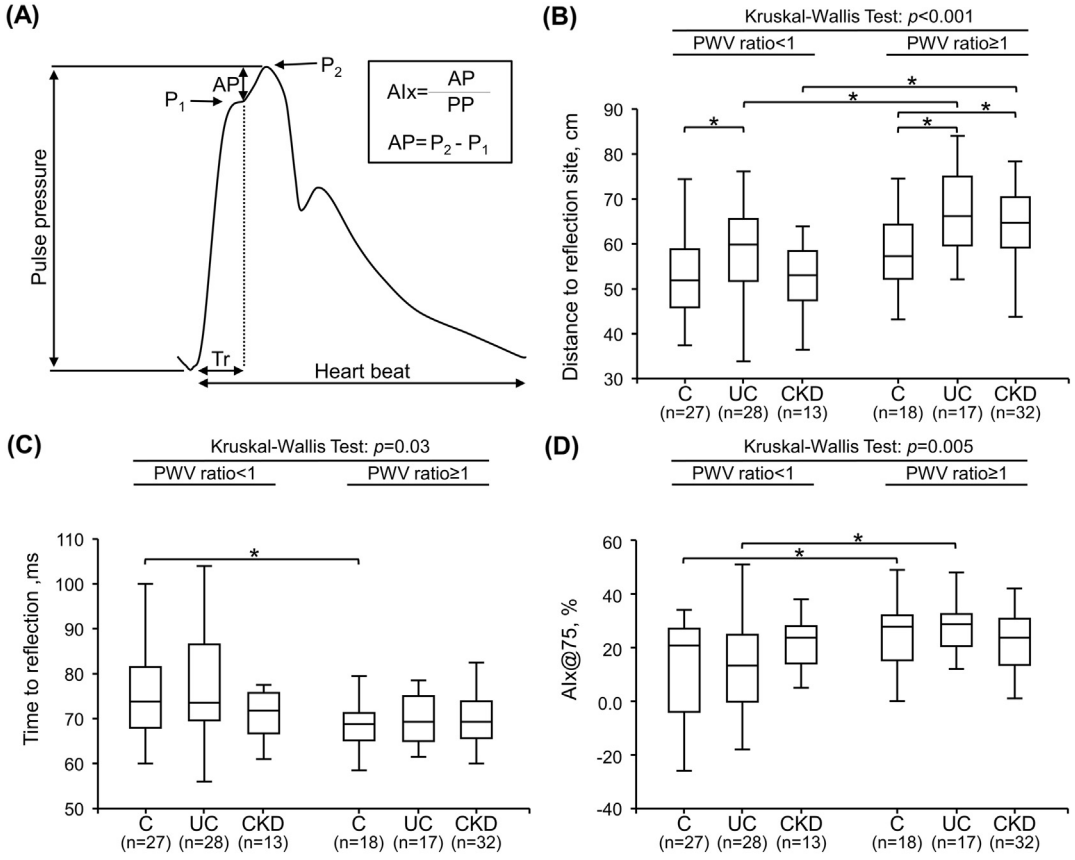

Fig. 1. Panel A: aortic pressure waves. **Panel B–D**: distance to reflection site, time to reflection (Tr/2) and augmentation index adjusted for heart rate (AIx@75) in controls (C), patients with ulcerative colitis (UC) and patients with chronic kidney disease (CKD) grouped by pulse wave velocity (PWV) ratio. Kruskal-Wallis Test with Dunn's test for multiple comparison. *$p < 0.05$. AP, augmentation pressure (reflected wave amplitude); AIx, augmentation index; P_1, early systolic pressure peak; P_2, late systolic pressure peak; PP, pulse pressure; PWV, pulse wave velocity; Tr, travel time.

Table 1
Main clinical data of the study population.

Variables	Controls ($n = 45$)	UC ($n = 45$)	CKD ($n = 45$)	p-Value[a]	Group's comparison*
Group	A	B	C		
Body mass index, kg/m^2	26 (20; 36)	24 (19; 30)	25 (21; 35)	0.04	A ≠ B
GFR, mL/min/1.73m^2	103 (74; 130)	102 (84; 130)	41 (16; 59)	<0.001	A ≠ C; B ≠ C
WBCs, 10^9/L	6.3 (4.3; 7.9)	6.7 (4.5; 10.5)	6.4 (4.4; 9.6)	0.03	A ≠ B
C-reactive protein, mg/L	1.4 (1.0–3.1)	6.9 (2.2–18.4)	3.8 (3.3–6.3)	<0.001	A ≠ B; A ≠ C
Neutrophils, 10^9/L	3.7 (2.4; 5.2)	4.4 (2.8; 7.8)	3.4 (2.4; 7.2)	0.01	A ≠ B; B ≠ C
N/L ratio	2.0 (1.3; 3.2)	2.5 (1.3; 6.3)	2.1 (1.0; 4.0)	0.03	A ≠ B; B ≠ C
Total cholesterol, mmol/L	182 (146; 213)	170 (126; 195)	199 (158; 214)	<0.001	B ≠ C
LDL, mmol/L	107 (71; 144)	95 (66; 128)	126 (76; 144)	<0.001	A ≠ B; B ≠ C
Plasma glucose, mg/dL	92 (80; 101)	88 (77; 102)	96 (82; 110)	0.01	B ≠ C
Peripheral PP, mm Hg	45 (32; 65)	50 (40; 65)	51 (37; 68)	0.02	A ≠ B; A ≠ C
Central PP, mm Hg	34 (20; 48)	37 (27; 53)	40 (25; 55)	0.02	A ≠ C
Distance to reflection site, cm	53 (44; 69)	62 (47; 81)	63 (47; 74)	0.001	A ≠ B; A ≠ C
cf-PWV, m/s	7.5 (5.6; 9.3)	8.5 (5.9; 10.2)	8.6 (6.9; 10.5)	0.001	A ≠ B; A ≠ C
cr-PWV, m/s	7.7 (6.0; 9.5)	8.7 (7.0; 10.2)	7.5 (6.1; 9.5)	<0.001	A ≠ B; B ≠ C
PWV ratio	0.97 (0.74; 1.25)	0.97 (0.79; 1.20)	1.12 (0.84; 1.45)	<0.001	A ≠ C
Medication					
ACEi/ARB, %	27	24	33	0.62	
Diuretics, %	7	4	24	0.01	
Salicylates, %	22	64	27	<0.001	
Steroids, %	0	33	0	<0.001	
Azathioprine, %	0	20	0	<0.001	
Anti TNF, %	0	22	0	<0.001	

Results are median (10–90 percentile) or %.
ACEi indicates angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blockers; cf.-PWV, carotid-femoral pulse wave velocity; CKD, chronic kidney disease; cr-PWV, carotid-radial pulse wave velocity; GFR, glomerular filtration rate; LDL, low-density lipoprotein; N/L, neutrophils/lymphocytes; PP, pulse pressure; PWV, pulse wave velocity; TNF, tumor necrosis factor; UC, ulcerative colitis; and WBCs, white blood cells.
[a] As appropriate, chi-square and Kruskal-Wallis tests.
* Dunn's test for multiple comparisons: $p < 0.05$.

Please cite this article as: Zanoli L, et al, Pulse wave velocity differs between ulcerative colitis and chronic kidney disease, Eur J Intern Med (2017), http://dx.doi.org/10.1016/j.ejim.2017.08.020

comparable in age, sex, heart rate, central DBP and MBP. No sex-based differences were reported. In patients with CKD, as expected, central PP was significantly higher than in controls. Patients with UC had a lower body mass index than control subjects and lower total cholesterol, low-density lipoprotein and plasma glucose levels than CKD patients. C-reactive protein, white blood cells, neutrophils and the neutrophil-to-lymphocyte ratio were significantly higher in patients with UC.

According to the study design, the UC and CKD patients were comparable in terms of cf.-PWV. However, cr-PWV was higher in UC patients than in control subjects and CKD patients (median 8.7, 7.7 and 7.5 m/s, respectively; $p < 0.001$). Consequently, the PWV ratio was higher in CKD patients than in controls and UC patients (median 1.12, 0.97 and 0.97, respectively; $p < 0.001$).

3.1. Hemodynamic variables and stiffness mismatch

Main hemodynamic variables in individuals with normal (PWV ratio < 1) and reverted stiffness gradient (PWV ratio ≥ 1) is reported in Fig. 1 Panel B-D. The distance to reflection site was increased whereas the time to reflection (Tr/2, Fig. 1 Panel A) remains almost unchanged in patients with UC and CKD with reverted stiffness gradient. Respect to patients with CKD, in those with UC the distance to reflection was increased in presence of normal stiffness gradient and comparable in presence of reverted stiffness. Salicylates dose varies from 100 mg/die in controls and patients with CKD to 1600–4000 mg/die in patients with UC.

3.2. Association between aortic and brachial stiffness

In Fig. 2 Panel A is reported the association between cf.-PWV and cr-PWV. Brachial stiffness (cr-PWV) increased substantially more with aortic stiffening (cf-PWV) in patients with UC than in those with CKD (Potthoff analysis: $p = 0.001$).

3.3. Determinants of the PWV ratio

Despite the PWV ratio being positively associated with age in all groups (Fig. 2 Panel B), the PWV ratio increased more by aging in patients with CKD than in those with UC (Potthoff analysis: $p = 0.01$). This was mostly explained by the higher increase of cr-PWV by aging in patients with UC than in those with CKD (Fig. 2 Panel D; Potthoff analysis: $p = 0.01$).

In patients with UC, the PWV ratio increased according to disease duration, C-reactive protein and active disease (Fig. 3 Panel A–C). In multivariate linear regression analysis, the PWV ratio was positively associated with age and, alternatively, C-reactive protein or active disease (Table 2).

In patients with CKD, the PWV ratio increased according to the severity of renal dysfunction from stage 3A CKD to stage 4 CKD ($p < 0.001$; Fig. 4 Panel A); this increase was largely due to the increase in cf.-PWV ($p < 0.001$; Fig. 4 Panel B) and the parallel lack of increase in cr-PWV by CKD stage ($p = 0.99$; Fig. 4 Panel C). In multivariate linear regression analysis, the PWV ratio was positively associated with age and GFR (Table 2).

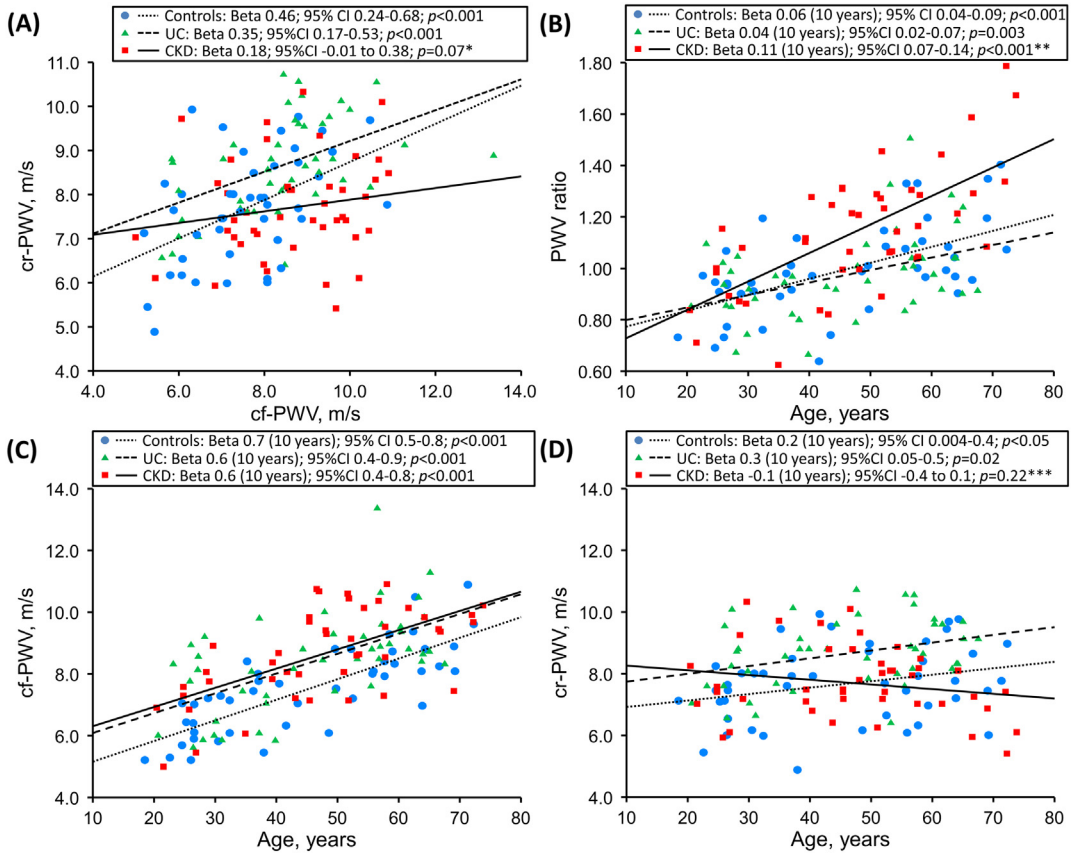

Fig. 2. Panel A, Association between carotid femoral pulse wave velocity (cf-PWV) and carotid-radial pulse wave velocity (cr-PWV) in controls, patients with ulcerative colitis (UC) and patients with chronic kidney disease (CKD). **Panel B–D**, association between age and pulse wave velocity (PWV) ratio, carotid-femoral PWV (cf-PWV) or carotid-radial PWV (cr-PWV) in controls, patients with ulcerative colitis (UC) and chronic kidney disease (CKD). Potthoff analysis: *cr-PWV increased substantially more with cf.-PWV in controls than in patients with CKD ($p < 0.001$); **PWV ratio increased substantially more with age in patients with CKD than in those with UC ($p = 0.01$); ***cr-PWV increased substantially more with age in patients with UC than in those with CKD ($p = 0.01$).

Please cite this article as: Zanoli L, et al, Pulse wave velocity differs between ulcerative colitis and chronic kidney disease, Eur J Intern Med (2017), http://dx.doi.org/10.1016/j.ejim.2017.08.020

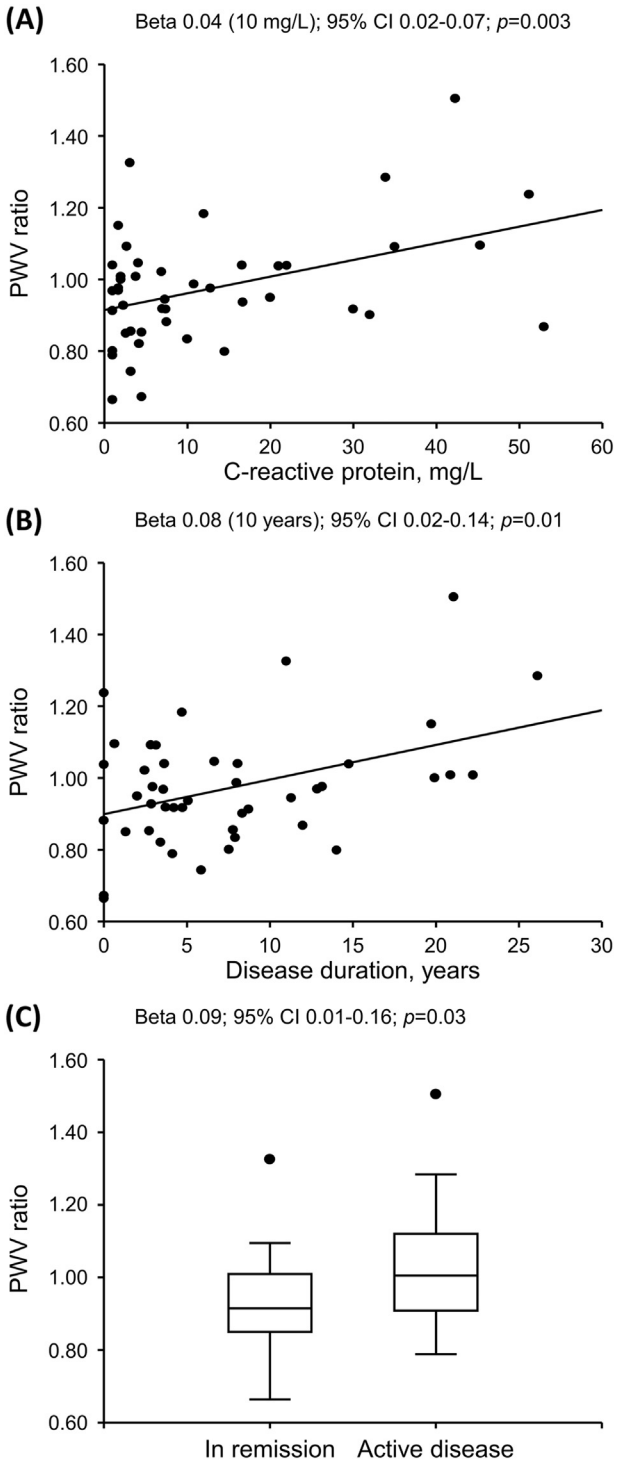

Fig. 3. Association between pulse wave velocity (PWV) ratio and C-reactive protein (**Panel A**), disease duration (**Panel B**), or active disease (**Panel C**) in patients with ulcerative colitis.

Table 2
Multivariate analysis. Clinical and biochemical determinants of the PWV ratio.

Determinants of PWV ratio	z-score	Beta	*p*-Value	Model R^2
Controls				
Age, 10 years	0.55 (0.32; 0.79)	0.06 (0.04; 0.09)	<0.001	0.346
UC				
Model A				
Age, 10 years	0.32 (0.07; 0.57)	0.04 (0.01; 0.06)	0.01	0.301
C-reactive protein, 10 mg/L	0.08 (0.02; 0.14)	0.04 (0.01; 0.07)	0.01	
Model B				
Age, 10 years	0.35 (0.11; 0.59)	0.04 (0.01; 0.06)	0.01	0.279
Active disease, yes	0.43 (0.003; 0.857)	0.08 (0.001; 0.150)	0.048	
CKD				
Age, 10 years	0.76 (0.39; 1.14)	0.08 (0.04; 0.12)	<0.001	0.518
GFR, 15 mL/min/1.73 m^2	−0.56 (−1.05; −0.07)	−0.07 (−0.13; −0.01)	0.02	

Outlier-robust multivariate linear regressions show the variables that were significantly associated with the PWV ratio. CKD indicates chronic kidney disease; GFR, glomerular filtration rate; PWV, pulse wave velocity; UC, ulcerative colitis.

4. Discussion

4.1. Arterial phenotype in patients with UC

The arterial phenotype of patients with UC was different from that of patients with CKD and control subjects. Indeed, for comparable aortic stiffness, brachial stiffness was significantly higher in UC than in CKD patients and control subjects. Also, the carotid remodeling seems to be different between IBD and CKD since in previous studies intima-media thickness was higher in patients with IBD than in controls, but it was not increased in those with CKD during a follow-up of 3 years [17,27].

During the last years, it has been reported that several markers of inflammation are associated with increased arterial stiffness. The association between disease duration, a variable associated with chronic inflammation, and increased arterial stiffness in patients with UC is in accordance with previous data [11,12,28,29]; the association between acute inflammation and arterial stiffening has been previously reported in other models of inflammation [30]. Taken together, these findings suggest that, in contrast to physiological aging and accelerated aging reported in patients with CKD, in whom aortic, but not brachial stiffening was shown, in UC patients both elastic and muscular components of arterial tree could be affected by inflammation. Although the hypothesis of a different arterial phenotype in patients with high-grade inflammation must be confirmed in prospective studies, data of the present study are in agreement with previous observations in patients with IBD [11,12] and in those with rheumatoid arthritis, in whom an increase in elastic artery stiffness and a trend toward a muscular artery stiffening were observed [21]. Furthermore, the increase of both aortic and brachial stiffness in patients with IBD is also in agreement with the notion that in patients with inflammation arterial stiffness could be linked to reduced smooth muscle cell relaxation (*functional arterial stiffening*) or increased metalloproteinases, degradation of tissue inhibitor of matrix metalloproteinases, increased hypertrophy/reduced apoptosis and osteoblast marker expression of smooth muscle cells (*structural arterial stiffening*) [10]. By contrast, in CKD patients, a derangement of intrinsic elastic properties of the arterial wall appears secondary to calcification of elastic lamellae, increased extracellular matrix and collagen content [20].

4.2. Accelerated vascular aging in early stages CKD

In youth, the physiological stiffness gradient (aortic stiffness < brachial artery stiffness) helps to attenuate the transmission of the forward pressure wave into the microcirculation. During normal aging and ESRD, a condition characterized by accelerated vascular aging, there is an increase of central aortic stiffness, which leads to increased aortic PWV, earlier wave reflection and increased cardiac workload and left ventricular hypertrophy [1], non-counterbalanced by an increase in peripheral brachial stiffness [31–33]. Interestingly, in patients on hemodialysis the brachial stiffness can be also reduced when the aortic stiffness is increased [10]. This mechanism, reducing the backward wave reflections, could be seen as an attempt to mitigate the effects of increased central aortic stiffness on central blood pressure. However, it is also potentially deleterious for the peripheral target organs, because

Please cite this article as: Zanoli L, et al, Pulse wave velocity differs between ulcerative colitis and chronic kidney disease, Eur J Intern Med (2017), http://dx.doi.org/10.1016/j.ejim.2017.08.020

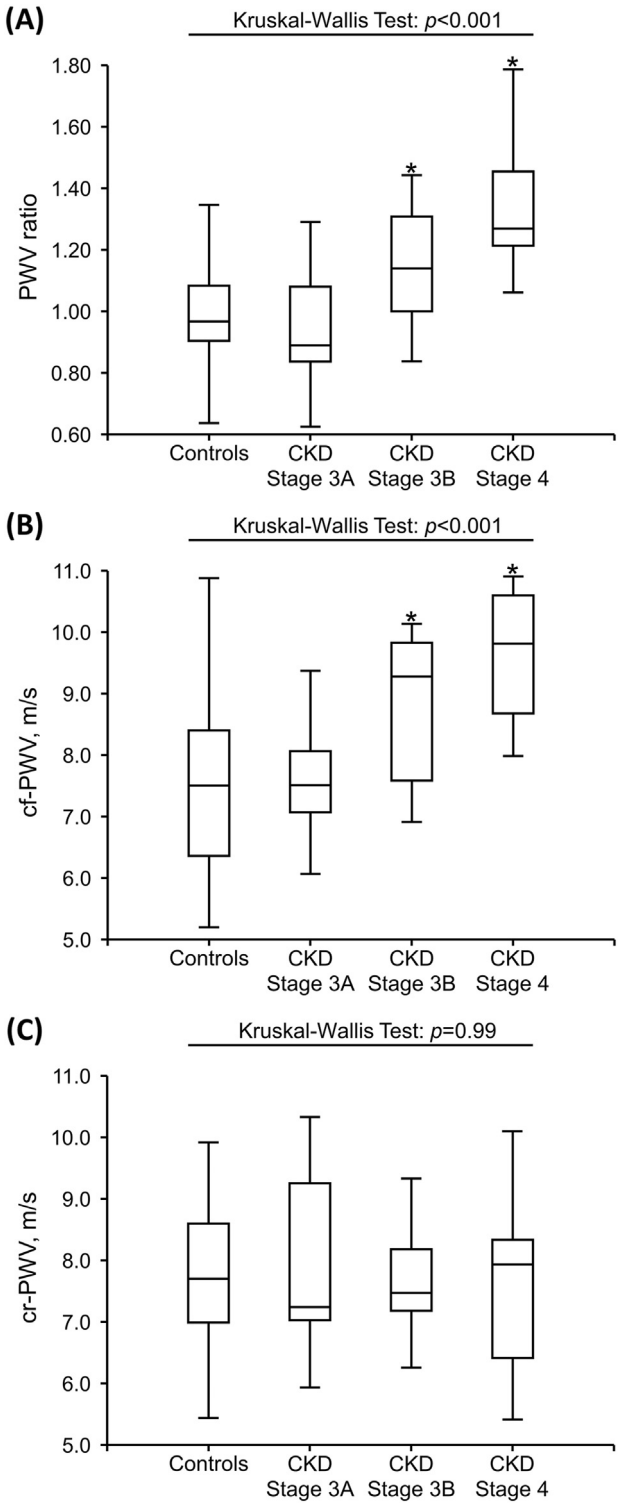

Fig. 4. Pulse wave velocity (PWV) ratio (**Panel A**), carotid-femoral PWV (cf-PWV) (**Panel B**) and carotid-radial PWV (cr-PWV) (**Panel C**) in controls and in patients with chronic kidney disease (CKD) classified according to the stage of CKD. Kruskal-Wallis Test with Dunn's test for multiple comparison. *$p < 0.05$ vs. controls and CKD stage 3A.

it increases the transmission of forward waves to the microcirculation. This may help to explain why the stiffness mismatch is a more powerful prognostic indicator of mortality than aortic stiffness, central pulse pressure, pulse pressure amplification or augmentation index in hemodialysis patients [9].

In accordance with a previous report [34], we demonstrated that the distance to reflection site was higher in patients with UC and those with CKD with a reversed aortic-brachial arterial stiffness gradient (Fig. 1 Panel B). Interestingly, the time to reflection was comparable in UC and CKD patients with stiffness mismatch (Fig. 1 Panel C), suggesting that the greater travel distance was counterbalanced by increased aortic stiffness. Moreover, the stiffness mismatch was associated with a greater Aix@75 (Fig. 1 Panel D) in patients with UC, indicating an increase of wave reflections, left ventricular afterload and myocardial oxygen demand.

4.3. Methodological issues

This study has some limitations. First, it is a cross-sectional study; therefore, causation cannot be determined for any of the observed relationships. Moreover, whether the brachial stiffening in UC patients is the result of a change in elastic properties of the arterial wall or of a change in the wall-to-lumen ratio remains unknown. Finally, the relatively small sample size and the cross-sectional design did not allow to evaluate the effect of antihypertensive and immunosuppressive drugs on the elastic/muscular artery stiffness gradient. Further to the present proof of concept study, future larger prospective surveys are necessary to explore these issues.

4.4. Perspectives

Current guidelines underline the importance of aortic stiffening in the pathogenesis and risk prediction of cardiovascular diseases. However, the importance of the central elastic/peripheral muscular artery stiffness gradient in the pathogenesis of cardiovascular diseases is currently understated. Considering that the stiffness mismatch increases the transmission of the forward pressure wave into the microcirculation, it could be of interest to assess whether the arterial phenotype of patients with UC, characterized by an increase of elastic and muscular artery stiffness, either protects from or, otherwise, enhances microcirculation damage. In this regard, both endothelial dysfunction and microcirculation damage have been previously reported in UC patients [17,36], and can by themselves contribute to the progression of vascular dysfunction in UC.

Finally, IBD represents a model in which the effects of inflammation on arterial stiffening, and the development of cardiovascular diseases, can be studied in the presence of a low prevalence of traditional cardiovascular risk factors.

5. Conclusions

The arterial phenotype of UC is different from that of CKD. In patients with UC, the stiffness of both elastic and muscular arteries is increased likely as a consequence of inflammation. Moreover, in patients with CKD the stiffness mismatch starts earlier, namely from stage 3B CKD.

Conflict of interest

The Authors declare that there is no conflict of interest.

Funding

This study was partially supported by the Ministry of Health, Italy (GR-2011-02349066).

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ejim.2017.08.020.

References

[1] Karras A, Haymann JP, Bozec E, et al. Large artery stiffening and remodeling are independently associated with all-cause mortality and cardiovascular events in chronic kidney disease. Hypertension 2012;60(6):1451–7.

[2] van der Heijden-Spek JJ, Staessen JA, Fagard RH, Hoeks AP, Boudier HA, van Bortel LM. Effect of age on brachial artery wall properties differs from the aorta and is gender dependent: a population study. Hypertension 2000;35:637–42.

[3] McEniery CM, Yasmin Hall IR, Qasem A, Wilkinson IB, Cockcroft JR. ACCT Investigators. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). J Am Coll Cardiol 2005;46:1753–60.

[4] Mitchell GF, Wang N, Palmisano JN, et al. Hemodynamic correlates of blood pressure across the adult age spectrum: noninvasive evaluation in the Framingham Heart Study. Circulation 2010;122:1379–86.

[5] Mitchell GF, Parise H, Benjamin EJ, et al. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. Hypertension 2004;43:1239–45.

[6] Liao D, Cooper L, Cai J, et al. The prevalence and severity of white matter lesions, their relationship with age, ethnicity, gender, and cardiovascular disease risk factors: the ARIC Study. Neuroepidemiology 1997;16:149–62.

[7] Safar ME, London GM, Plante GE. Arterial stiffness and kidney function. Hypertension 2004;43:163–8.

[8] Mitchell GF. Increased aortic stiffness: an unfavorable cardiorenal connection. Hypertension 2004;43:151–3.

[9] Fortier C, Mac-Way F, Desmeules S, et al. Aortic-brachial stiffness mismatch and mortality in dialysis population. Hypertension 2015;65(2):378–84.

[10] Zanoli L, Rastelli S, Inserra G, Castellino P. Arterial structure and function in inflammatory bowel disease. World J Gastroenterol 2015;21(40):11304–11.

[11] Zanoli L, Cannavò M, Rastelli S, et al. Arterial stiffness is increased in patients with inflammatory bowel disease. J Hypertens 2012;30(9):1775–81.

[12] Zanoli L, Rastelli S, Inserra G, et al. Increased arterial stiffness in inflammatory bowel diseases is dependent upon inflammation and reduced by immunomodulatory drugs. Atherosclerosis 2014;234(2):346–51.

[13] Zanoli L, Rastelli S, Granata A, et al. Arterial stiffness in inflammatory bowel disease: a systematic review and meta-analysis. J Hypertens 2016;34(5):822–9.

[14] Zanoli L, Boutouyrie P, Lentini P, Rastelli S, Castellino P. Maintenance therapy with salicylates is associated with aortic stiffening in patients with inflammatory bowel disease. J Hypertens 2017;35(4):898–9.

[15] Zanoli L, Granata A, Lentini P, Gaudio A, Castellino P. Augmentation index is increased in patients with inflammatory bowel disease, a meta-analysis. Eur J Intern Med 2017;39:e31-.

[16] Zanoli L, Signorelli SS, Inserra G, Castellino P. Subclinical atherosclerosis in patients with inflammatory bowel diseases: a systematic review and meta-analysis. Angiology 2017;68(5):463.

[17] Wu GC, Leng RX, Lu Q, Fan YG, Wang DG, Ye DQ. Subclinical atherosclerosis in patients with inflammatory bowel diseases: a systematic review and meta-analysis. Angiology 2017;68(5):447–61.

[18] Harbord M, Annese V, Vavricka SR, et al. The first European evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. J Crohns Colitis 2016;10(3):239–54.

[19] Zanoli L, Inserra G, Castellino P. Increased cardiovascular risk in subjects with a low prevalence of classic cardiovascular risk factors: the inflammatory bowel disease paradox. Trends Cardiovasc Med 2015;25(8):705–6.

[20] Guérin AP, Pannier B, Métivier F, Marchais SJ, London GM. Assessment and significance of arterial stiffness in patients with chronic kidney disease. Curr Opin Nephrol Hypertens 2008;17:635–41.

[21] Ambrosino P, Tasso M, Lupoli R, et al. Non-invasive assessment of arterial stiffness in patients with rheumatoid arthritis: a systematic review and meta-analysis of literature studies. Ann Med 2015;47(6):457–67.

[22] Van Bortel LM, Laurent S, Boutouyrie P, et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. J Hypertens 2012;30:445–8.

[23] Chen CH, Nevo E, Fetics B, et al. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function. Circulation 1997;95:1827–36.

[24] Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150(9):604–12.

[25] Dignass A, Eliakim R, Magro F, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. J Crohns Colitis 2012;6(10):965–90.

[26] Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. Inflamm Bowel Dis 2008;14(12):1660–6.

[27] Briet M, Bozec E, Laurent S, et al. Arterial stiffness and enlargement in mild-to-moderate chronic kidney disease. Kidney Int 2006;69(2):350–7.

[28] Korkmaz H, Sahin F, Ipekci SH, Temel T, Kebapcilar L. Increased pulse wave velocity and relationship with inflammation, insulin, and insulin resistance in inflammatory bowel disease. Eur J Gastroenterol Hepatol 2014;26(7):725–32.

[29] Ozturk K, Guler AK, Cakir M, et al. Pulse wave velocity, intima media thickness, and flow-mediated dilatation in patients with normotensive normoglycemic inflammatory bowel disease. Inflamm Bowel Dis 2015;21(6):1314–20.

[30] Vlachopoulos C, Dima I, Aznaouridis K, et al. Acute systemic inflammation increases arterial stiffness and decreases wave reflection in healthy individuals. Circulation 2005;112:2193–200.

[31] Zhang Y, Agnoletti D, Protogerou AD, et al. Characteristics of pulse wave velocity in elastic and muscular arteries: a mismatch beyond age. J Hypertens 2013;31:554–9.

[32] Avolio AP, Chen SG, Wang RP, Zhang CL, Li MF, O'Rourke MF. Effects of aging on changing arterial compliance and left ventricular load in a northern Chinese urban community. Circulation 1983;68:50–8.

[33] Mitchell GF, Vita JA, Larson MG, et al. Cross-sectional relations of peripheral microvascular function, cardiovascular disease risk factors, and aortic stiffness: the Framingham Heart Study. Circulation 2005;112:3722–8.

[34] Hickson SS, Nichols WW, Yasmin, et al. Influence of the central-to-peripheral arterial stiffness gradient on the timing and amplitude of wave reflections. Hypertens Res 2016;39(10):723–9.

[35] Stancanelli B, Malatino LS, Malaponte G, et al. Pulse pressure is an independent predictor of aortic stiffness in patients with mild to moderate chronic kidney disease. Kidney Blood Press Res 2007;30(5):283–8.

[36] Danese S, Sans M, de la Motte C, et al. Angiogenesis as a novel component of inflammatory bowel disease pathogenesis. Gastroenterology 2006;130(7):2060–73.

Please cite this article as: Zanoli L, et al, Pulse wave velocity differs between ulcerative colitis and chronic kidney disease, Eur J Intern Med (2017), http://dx.doi.org/10.1016/j.ejim.2017.08.020