Pulse wave velocity differs between ulcerative colitis and chronic kidney disease

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A B S T R A C T

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.

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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...
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, methodological 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 inter-session 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 application 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 centralised 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 Pothoff analysis was used to compare regression lines. We performed an 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
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; P1, early systolic pressure peak; P2, late systolic pressure peak; PP, pulse pressure; PWV, pulse wave velocity; Tr, travel time.

Table 1
Main clinical data of the study population.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls (n = 45)</th>
<th>UC (n = 45)</th>
<th>CKD (n = 45)</th>
<th>p-Value⁵</th>
<th>Group’s comparison⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26 (20; 36)</td>
<td>24 (19; 30)</td>
<td>25 (21; 35)</td>
<td>0.04</td>
<td>A ≠ B</td>
</tr>
<tr>
<td>GFR, mL/min/1.73m²</td>
<td>103 (74; 130)</td>
<td>102 (84; 130)</td>
<td>41 (16; 59)</td>
<td>&lt;0.001</td>
<td>A ≠ C; B ≠ C</td>
</tr>
<tr>
<td>WBCs, 10⁹/L</td>
<td>6.3 (4.3; 7.9)</td>
<td>6.7 (4.5; 10.5)</td>
<td>6.4 (4.4; 9.6)</td>
<td>0.03</td>
<td>A ≠ B</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>1.4 (1.0–3.1)</td>
<td>6.9 (2.2–18.4)</td>
<td>3.8 (3.3–6.3)</td>
<td>&lt;0.001</td>
<td>A ≠ B; A ≠ C</td>
</tr>
<tr>
<td>Neutrophils, 10⁹/L</td>
<td>3.7 (2.4–5.2)</td>
<td>4.4 (2.8–7.8)</td>
<td>3.4 (2.4–7.2)</td>
<td>0.01</td>
<td>A ≠ B; B ≠ C</td>
</tr>
<tr>
<td>N/L ratio</td>
<td>2.0 (1.3–3.2)</td>
<td>2.5 (1.3–6.3)</td>
<td>2.1 (1.0–4.0)</td>
<td>0.03</td>
<td>A ≠ B; B ≠ C</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>182 (146; 213)</td>
<td>170 (126; 195)</td>
<td>199 (158; 214)</td>
<td>&lt;0.001</td>
<td>B ≠ C</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>107 (71; 144)</td>
<td>95 (66; 128)</td>
<td>126 (76; 144)</td>
<td>&lt;0.001</td>
<td>A ≠ B; B ≠ C</td>
</tr>
<tr>
<td>Plasma glucose, mg/dL</td>
<td>92 (80; 101)</td>
<td>88 (77; 102)</td>
<td>96 (82; 110)</td>
<td>0.01</td>
<td>B ≠ C</td>
</tr>
<tr>
<td>Peripheral PP, mm Hg</td>
<td>45 (32; 65)</td>
<td>50 (40; 65)</td>
<td>51 (37; 68)</td>
<td>0.02</td>
<td>A ≠ B; A ≠ C</td>
</tr>
<tr>
<td>Central PP, mm Hg</td>
<td>34 (20; 48)</td>
<td>37 (27; 53)</td>
<td>40 (25; 55)</td>
<td>0.02</td>
<td>A ≠ C</td>
</tr>
<tr>
<td>Distance to reflection site, cm</td>
<td>53 (44; 69)</td>
<td>62 (47; 81)</td>
<td>63 (47; 74)</td>
<td>0.001</td>
<td>A ≠ B; A ≠ C</td>
</tr>
<tr>
<td>cf-PWV, m/s</td>
<td>7.5 (5.6; 9.3)</td>
<td>8.5 (5.9; 10.2)</td>
<td>8.6 (6.9; 10.5)</td>
<td>0.001</td>
<td>A ≠ B; A ≠ C</td>
</tr>
<tr>
<td>cr-PWV, mm/s</td>
<td>7.7 (6.0; 9.5)</td>
<td>8.7 (7.0; 10.2)</td>
<td>7.5 (6.1; 9.5)</td>
<td>&lt;0.001</td>
<td>A ≠ B; B ≠ C</td>
</tr>
<tr>
<td>PWV ratio</td>
<td>0.97 (0.74; 1.25)</td>
<td>0.97 (0.79; 1.20)</td>
<td>1.12 (0.84; 1.45)</td>
<td>&lt;0.001</td>
<td>A ≠ C</td>
</tr>
</tbody>
</table>

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.

⁵ As appropriate, chi-square and Kruskal-Wallis tests.

⁶ Dunn’s test for multiple comparisons: p < 0.05.
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. In patients with CKD, as expected, central PP was signifi-
cantly 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).
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 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...
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.

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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


