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

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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.

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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

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