Original Article

Arterial stiffness is increased in patients with inflammatory bowel disease

Luca Zanoli[a,b], Mariarita Cannavò[a], Stefania Rastelli[a], Luigi Di Pino[a], Ines Monte[a], Marcella Di Gangi[a], Pierre Boutouyrie[b], Gaetano Inserra[a], Stephane Laurent[b], and Pietro Castellino[a]

Background and aims: Recent studies have reported early atherosclerosis in patients with inflammatory bowel disease (IBD). In these patients, the chronic low-grade inflammation may predispose to vascular remodelling and arterial stiffening. We aimed at studying arterial stiffness in IBD patients.

Methods: Thirty-two IBD patients without cardiovascular risk factors and 32 matched controls were enrolled (age 19–49 years). SphygmoCor device (AtCor Medical, Sydney, Australia) was used to measure carotid–femoral and carotid–radial (muscular artery) pulse wave velocity (PWV), augmentation index and central blood pressure.

Results: Carotid–femoral PWV was higher in IBD patients than in controls (6.6 ± 1.4 vs. 6.0 ± 0.8 m/s, respectively, $P < 0.05$), as well as carotid–radial PWV (8.5 ± 1.2 vs. 7.2 ± 1.0 m/s, $P < 0.001$). Central pulse pressure was higher in IBD than in controls (32 ± 6 vs. 28 ± 7 mmHg, $P < 0.05$). Aging was an important determinant of carotid–femoral PWV in both groups and carotid–radial PWV only in IBD patients. In fully adjusted model performed in both groups of patients considered as a whole, age was positively associated with carotid–femoral PWV [$R^2 = 0.10$; +0.05 m/s per 1 year of aging, 95% confidence interval (CI) 0.01–0.08 m/s, $P < 0.05$], as well as IBD ($R^2 = 0.10$; +0.72 m/s if IBD present, 95% CI 0.19–1.26 m/s, $P < 0.05$). In IBD patients, carotid–radial PWV was positively associated with the disease duration ($R^2 = 0.20$; +0.11 m/s per 1 year of aging, 95% CI 0.03–0.19 m/s, $P < 0.05$).

Conclusion: Arterial stiffness is increased in patients with IBD independently of conventional cardiovascular risk factors.

Keywords: central blood pressure, inflammation, pulse wave velocity

Abbreviations: AIx_{75}, Augmentation index corrected for a steady heart rate of 75 beats/min; CI, confidence interval; CRP, C-reactive protein; IBD, inflammatory bowel disease; PP, pulse pressure; PWV, pulse wave velocity

INTRODUCTION

Inflammatory bowel disease (IBD) is a group of inflammatory conditions of the colon and small intestine. In IBD, intestinal microvascular endothelial cells are damaged by an abnormal immune response resulting in chronic inflammation [1]. Recent studies reported early atherosclerosis [2], altered high-density lipoprotein [3], increased carotid intima–media thickness [4], elevated homocysteine [5] and insulin resistance [6] in patients with IBD. In addition, endothelium-dependent vasodilation is impaired [7] and a novel prostaglandin-mediated vasodilatory mechanism has been described in the gut of patients with IBD [8]. To our knowledge, few data are available on the arterial elastic properties in IBD [9], although various clinical models of chronic inflammatory diseases are associated with an increased arterial stiffness [10,11].

The role of arterial stiffness in the development of cardiovascular diseases is well known [12]. Arterial elastic properties are increasingly used for stratifying the cardiovascular risk in several populations; aortic pulse wave velocity (PWV) has predictive value for cardiovascular events and all-cause mortality independent of classic cardiovascular risk factors in the general population and in patients at high cardiovascular risk [13–16]; aortic stiffness is listed as a target organ damage to be detected in clinical practice, in the 2007 European guidelines for the management of hypertension and guidelines for cardiovascular disease prevention [17,18].

We hypothesized that IBD, which is characterized by both a chronic, subclinical, systemic inflammation and episodes of acute systemic inflammation during the reactivation of the disease is associated with an increased arterial stiffness. Our objective was thus to demonstrate that patients with IBD have a higher arterial stiffness than matched healthy controls, and that the systemic inflammation plays an important role in this process.

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[a]Department of Internal Medicine, University of Catania, Catania, Italy and [b]Department of Pharmacology, Hôpital Européen Georges Pompidou, Assistance Publique, Hôpitaux de Paris, INSERM U970, Paris Descartes University, Paris, France

Correspondence to Luca Zanoli, MD, Department of Pharmacology, Hôpital Européen Georges Pompidou, Assistance Publique, Hôpitaux de Paris, 20, rue Leblanc, Paris 75015, France. Tel: +33 156093991; fax: +33 156093992; e-mail: zanoli.rastelli@gmail.com

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METHODS

Study population

A total of 32 young IBD patients (16 patients with Crohn's disease and 16 patients with ulcerous colitis, age 19–49 years) without cardiovascular risk factors were enrolled and paired to 32 matched healthy controls. Exclusion criteria were hypertension, as defined by blood pressure at least 140/90 mmHg and/or use of antihypertensive medication; hyperlipidemia and/or use of lipid-lowering medication; diabetes mellitus and/or use of antidiabetic medication; heart failure, as defined by ventricular ejection fraction less than 50%; smoking; chronic kidney disease, defined as glomerular filtration rate less than 60 ml/min per 1.73 m^2; obesity, defined as BMI at least 30 kg/m^2; history of past cardiovascular or cerebrovascular events. The protocol was approved by the local ethics committee, in accordance with the Helsinki Declaration, and all participants gave written informed consent.

Study design

The diagnosis of IBD was based on established criteria of clinical, radiological, endoscopic and histological findings. Patients with IBD who met the inclusion criteria were included in this analysis. A control group was constituted by healthy individuals matched for age, sex, brachial blood pressure, heart rate, weight and height (case/control ratio = 1 : 1). The medical history of the patients, including the disease duration, was collected; a routine physical examination was conducted.

Hemodynamic measurements

The noninvasive investigation was performed in a dedicated room after 15 min of recumbent rest following the recommendations for standardization of participant conditions [12]. Brachial blood pressure measurements were taken every 2 min (Dinamap ProCare 100; GE Healthcare). Central pressures were recorded noninvasively by applanation tonometry (SphygmoCor; AtCor Medical, Sydney, Australia) as previously described and validated by comparison with simultaneous invasive pressure recordings [19–21]. Tonometry uses a transfer function from the radial to the aortic site, for estimating central blood pressure, and requires an absolute calibration performed with brachial cuff measurements of diastolic and mean blood pressure in the contralateral arm in order to determine the aortic pressure waveform [12].

An important physics principle is that the pulse travels at a higher velocity in a stiff vessel and more slowly in an elastic vessel. PWV, an established index of arterial stiffness [12,13,22] was measured by a well accepted device (SphygmoCor; AtCor Medical, Sydney, Australia) using the foot-to-foot velocity method. Briefly, waveforms were obtained transcutaneously over the common carotid artery and the right femoral or radial artery, and the delay was measured between the feet of the two waveforms. The distance covered by the waves was estimated subtracting the distance from the carotid location to the sternal notch from the distance between the sternal notch and the femoral or radial site of measurement [12]. The equation used in the present report for calculating PWV is as follows [12]:

$$\mathrm{PWV} = \frac{\text{subtracted distance (metres)}}{\text{delay (seconds)}}$$

Both carotid–femoral (aortic) and carotid–radial (muscular artery) PWV were measured.

The augmentation index represents a composite measure of the magnitude of wave reflection and arterial stiffness, which affects timing of wave reflections. The augmentation index was measured on the central pressure waves determined by applanation tonometry, averaged from 10 to 12 successive waves and corrected for a steady heart rate of 75 beats/min (AIx_{75}) [23].

RESULTS

The matching process worked well, patients and controls were comparable for age, sex ratio, blood pressure, heart rate, weight and height (Table 1).

Clinical characteristics of patients with inflammatory bowel disease

The characteristics of the populations are presented in Table 1. IBD patients were relatively young (30 ± 9 years) and predominantly men [19 (59%) men and 13 (41%) women). The mean disease duration was 63 ± 61 months (minimum to maximum 0–267 months). Healthy controls were well matched and there was no significant difference between IBD and controls regarding demographics (Table 1).

Main laboratory data of patients with IBD are reported in Table 2. The lipid profile and plasma glucose levels were in the normal range; mean erythrocyte sedimentation rate was 18 ± 10 mm/h; C-reactive protein (CRP) values fall in the normal range (<3 mg/l) for 88% of patients. All but one patient with active IBD had CRP levels above 3 mg/l, the maximum value being 5.15 mg/l.

Among IBD patients, 50% ($n = 16$) had ulcerative colitis and 50% ($n = 16$) had Crohn's disease. There were no differences between patients with ulcerative colitis and Crohn's disease regarding demographics and arterial parameters. Of IBD patients, 88% ($n = 28$) were in remission, whereas 12% ($n = 4$) had active disease; among patients with IBD, 66% ($n = 21$) had no gastrointestinal complication, whereas 22% ($n = 7$) had stricture, 25% ($n = 8$) had fistula and 22% ($n = 7$) had abscess. Of patients with Crohn's disease, 19% ($n = 3$) had complication outside the gastrointestinal tract (two patients with peripheral arthritis and one patient with erythema nodosum). Of patients with ulcerative colitis, 6% ($n = 1$) had complication outside the gastrointestinal tract (one patient with erythema nodosum). Among IBD patients, 38% ($n = 12$) were treated with only salicylates, whereas the remaining 62% ($n = 20$) were treated by salicylates and steroids or immunosuppressors.

Arterial parameters

Brachial blood pressure and heart rate were comparable in patients with IBD and in controls. For a comparable central mean blood pressure (Fig. 1, Panel b), IBD patients had a

TABLE 1. Main clinical data of study population

Parameters	IBD	Controls M (SD)	*P* M (SD)
Patients, *n*	32	32	
Age, years	30 (9)	31 (7)	NS
Male sex, %	59	59	NS
Weight (kg)	67.1 (14.0)	69.0 (12.6)	NS
Height (m)	1.68 (0.10)	1.68 (0.10)	NS
BMI (kg/m^2)	23.5 (3.6)	24.3 (2.8)	NS
Heart rate beats/min	68 (9)	65 (10)	NS
Brachial SBP (mmHg)	115 (10)	113 (11)	NS
Brachial DBP (mmHg)	66 (10)	68 (8)	NS
Brachial PP (mmHg)	49 (10)	45 (11)	NS
Brachial MBP (mmHg)	82 (9)	83 (7)	NS
Central SBP (mmHg)	99 (11)	97 (8)	NS
Central DBP (mmHg)	67 (11)	69 (9)	NS
Central PP (mmHg)	32 (6)	28 (7)	<0.05
Central MBP (mmHg)	81 (10)	80 (9)	NS
Carotid–femoral PWV (m/s)	6.6 (1.4)	6.0 (0.8)	<0.05
Carotid–radial PWV (m/s)	8.5 (1.2)	7.2 (1.0)	<0.001
Augmentation index (%)	7.4 (10.5)	1.5 (15.4)	NS

MBP, mean blood pressure; PP, pulse pressure; PWV, pulse wave velocity.

higher central pulse pressure (PP) (32 ± 6 vs. 28 ± 7 mmHg, respectively, P<0.05; Fig. 1, Panel a) and a higher carotid–femoral PWV than controls (6.6 ± 1.4 vs. 6.0 ± 0.8 m/s, $P < 0.05$; Fig. 1, Panel c). AIx_{75} was not significantly increased in IBD. Carotid–femoral PWV was higher in IBD than in controls (6.6 vs. 6.0 m/s, $P < 0.05$). Among patients with IBD, patients in the higher quartile of CRP (CRP$\geq$1.32 mg/l) have higher carotid–femoral PWV (7.3 ± 2.0 vs. 6.4 ± 1.0 m/s). However, this difference doesn't reach a significant level ($P = 0.10$). Carotid–radial PWV was higher in patients with active disease than in those without active disease (9.5 ± 1.3 and 7.7 ± 1.2 m/s respectively, $P < 0.05$). A significant relationship between age and carotid–femoral PWV was observed in both patients with IBD and controls (Fig. 2, Panel b), whereas a significant relationship between age and carotid–radial PWV was observed only in IBD (Fig. 2, Panel b) and confirmed even after adjustment for use of steroids or immunosuppressors and activity of disease (PWV = $5.64 + 0.09 \times$ age, $P < 0.001$, Table 3). Carotid–radial PWV was higher in patients with IBD than in controls (8.5 vs 7.2 m/s, $P < 0.001$). A significant relationship was observed between the disease duration and carotid–radial PWV (Fig. 3, Panel a). Between patients with ulcerative colitis and Crohn's disease, no significant difference in carotid–femoral PWV (6.8 vs. 6.5 m/s, respectively, NS) and in carotid–radial PWV (8.7 vs. 8.3 m/s, NS) was observed.

In multiple regression analysis involving the entire population (Table 3), IBD was a significant determinant of carotid–femoral PWV, explained 10% of its variance, even after adjustment for age, use of steroids or immunosuppressors and activity of disease. The presence of an IBD shifted the age–PWV relationship upward (Fig. 2, Panel b) by 0.72 m/s. In the fully adjusted model performed in both groups of patients considered as a whole, age was positively associated with carotid–femoral PWV [$R^2 = 0.10 + 0.05$ m/s per 1 year of aging, 95% confidence interval (CI) 0.01–0.08 m/s, $P < 0.05$], as well as IBD ($R^2 = 0.10 + 0.72$ m/s if IBD present, 95% CI 0.19–1.26 m/s, $P < 0.05$). Filtering patients with active disease did not change the results.

TABLE 2. Main laboratory data of patients with inflammatory bowel disease

Parameters	Values
Total cholesterol (mg/dl)	162 ± 26
LDL cholesterol (mg/dl)	95 ± 17
HDL cholesterol (mg/dl)	46 ± 13
Plasma glucose (mg/dl)	86 ± 8
C-reactive protein (mg/l)	0.57 (0.35–1.32)
Erythrocyte sedimentation rate (mm/h)	18 ± 10

HDL, high-density lipoprotein; LDL, low-density lipoprotein. Data are reported as mean $\pm$ SD or median (interquartile range), as appropriate.

DISCUSSION

This is the first study designed to determine arterial stiffness in young IBD patients without known cardiovascular risk factors. The major result of this study is that the stiffness of elastic and muscular arteries is increased in IBD patients compared with matched healthy controls.

Interpretation of the data

The stiffness of both elastic and muscular arteries is increased in patients with IBD. Several mechanisms can play a role in this process. It is well known that the level of inflammation could be related to both carotid–femoral and carotid–radial PWV [24–26]. Recent studies have reported an association between chronic low-grade inflammation and arterial stiffening [10,11]. Systemic inflammation, thus, appears as an emerging causal factor for increased arterial stiffness in chronic inflammatory disease states such as systemic vasculitis [11], systemic lupus erythematosus [10], rheumatoid arthritis [10] and HIV [27]. Moreover, it has been reported that even an acute, mild, transient

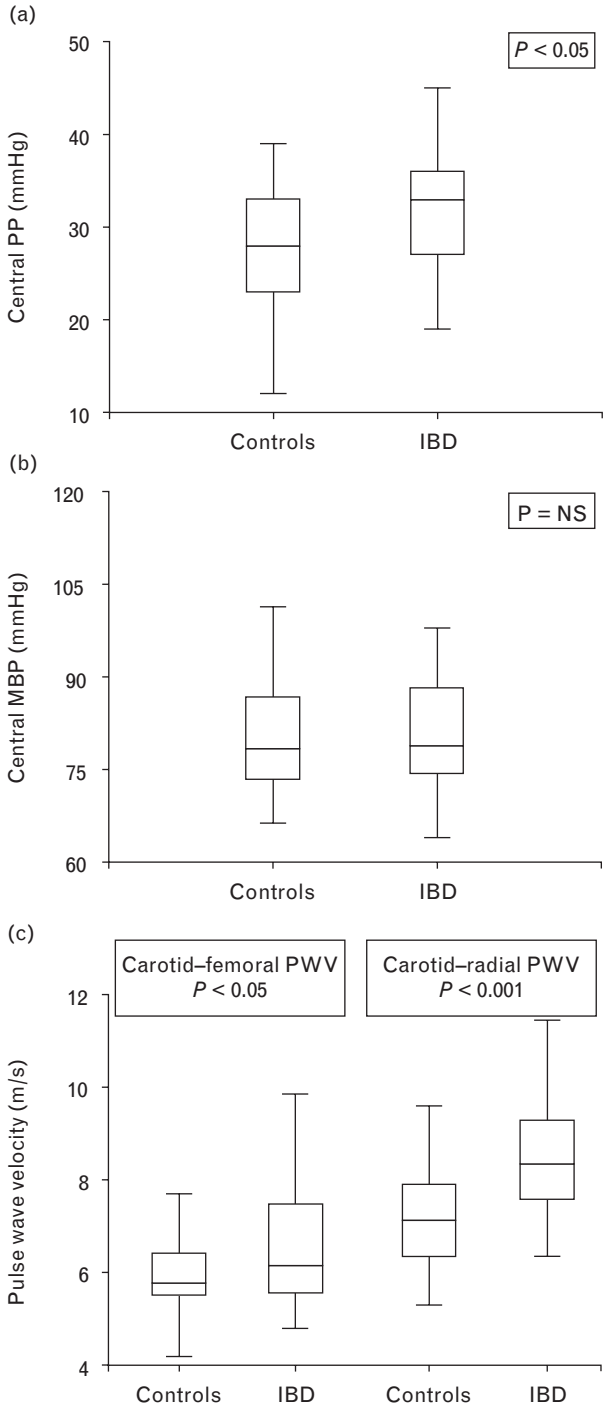

FIGURE 1 Panel (a) Central pulse pressure, Panel (b) central mean blood pressure (MBP) and Panel (c) arterial stiffness in patients with inflammatory bowel disease (IBD) and in controls.

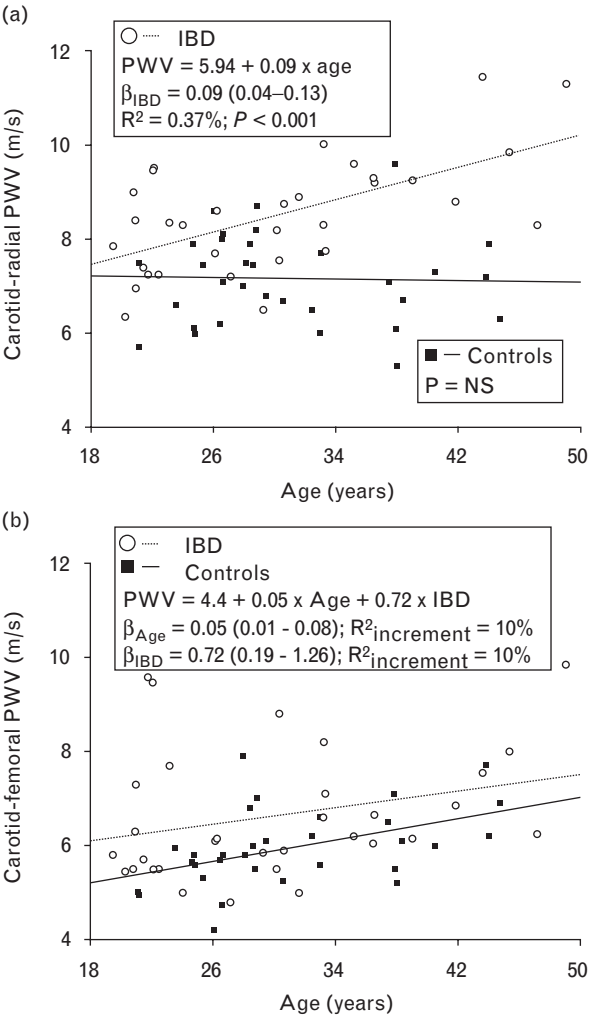

FIGURE 2 Relationship between age of the patients and arterial stiffness. Panel (a) carotid–radial (muscular artery) pulse wave velocity (PWV); Panel (b) carotid–femoral (aortic) PWV.

inflammatory stimulus may lead to deterioration of large artery elastic properties [28]. However, the arterial stiffening in chronic inflammatory disorders can be independent of the presence of atherosclerosis and related to disease duration [10] or, alternatively, can be a manifestation of vascular disease preceding. Several mechanisms by which a systemic inflammatory state can accelerate the atherosclerotic process have been suggested. Cytokine-mediated damaging of the endothelium, immune cell activation and activation of the coagulation cascade have all been implicated. IBD seems to be the result of a combination of environmental, genetic and immunologic factors in which an uncontrolled immune response within the intestine leads to inflammation in genetically predisposed individuals [29]. Dysfunctions of the intestinal immune system and cross-reactivity against host epithelial cells have been implicated as major mechanisms by which inflammation occurs [30]. Early atherosclerosis is a clinical feature common to several inflammatory and immunological diseases [30]. Several reports have suggested that IBD is associated with premature atherosclerosis by demonstrating intima-media thickness thickening [2,4] and endothelial dysfunction [7]. The latter seems to improve after administration of tumor necrosis factor-α antagonist [31].

Many studies reported that the prevalence of classical cardiovascular risk factors is lower in patients with IBD than in the general population [3,32–35]. Low BMI and lipid levels were previously seen in IBD patients [32–35]. IBD patients had also significantly lower rates of hypertension,

TABLE 3. Determinants of arterial stiffness

Parameters	R^2 increment	β coefficient (m/s)	Lower CI	Upper CI	*P*
IBD patients and controls considered as a whole					
Dependent variable: carotid–femoral PWV[a]					
Age (years)	0.11	0.05	0.01	0.09	<0.05
IBD	0.10	0.90	0.23	1.58	<0.05
$R^2 = 0.20$					
IBD patients					
Dependent variable: carotid–radial PWV[a]					
Age (years)	0.31	0.09	0.04	0.13	<0.001
$R^2 = 0.41$					

CI, confidence interval; IBD, inflammatory bowel disease; PWV, pulse wave velocity.
[a]Adjusted for use of steroids or immunosuppressors (yes/no) and activity of disease (yes/no).

diabetes and obesity [35]. Therefore, given the risk profile of patients with IBD, cardiovascular morbidity and mortality should be lower in these patients than in the general population. However, a meta-analysis reported that the standardized mortality ratio is not reduced in IBD patients [36]; recent studies reported an increased risk of coronary artery disease in IBD patients [35,37]. We think that IBD represents a useful model to study the effect of chronic low-grade inflammation in the development of cardiovascular diseases. In patients with IBD, the low cardiovascular risk associated with the low prevalence of cardiovascular risk factors may offset the increased cardiovascular risk associated with chronic inflammation. A better comprehension of these concomitant and inverse effects, mostly not considered in the cardiovascular risk stratification of IBD patients, could help to clarify whether IBD is associated or not with an increased cardiovascular risk. In this regards, the arterial stiffening could represents a link between chronic inflammation and cardiovascular risk in IBD patients.

Another important finding of this report is the significant increase of carotid–radial PWV according with the disease duration. This finding is clinically relevant and may help to understand the association between inflammation and arterial stiffening. Disease duration can be considered a marker of inflammation; therefore, patients with longer disease duration were exposed to a significantly higher amount of inflammation than patients with short disease duration. Interestingly, carotid–radial PWV, but not carotid–femoral PWV, was significantly increased according with the disease duration. These findings suggest different mechanisms in the stiffening of elastic and muscular arteries in response to aging and inflammation.

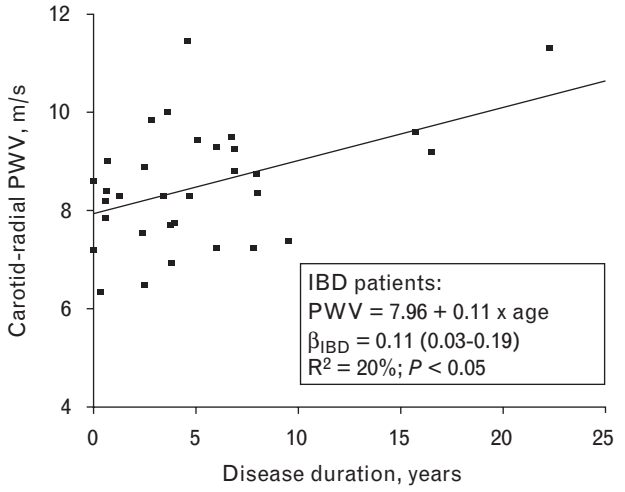

FIGURE 3 Relationship between disease duration and carotid–radial (muscular artery) pulse wave velocity (PWV).

Indeed, in the present study, chronic inflammation (i.e. IBD) increased aortic stiffness at any given age suggesting that arterial stiffening provided by IBD was additive to that of normal aging, representing a 14 years acceleration. Aging is associated with a number of molecular changes of the load-bearing media of elastic arteries: the orderly arrangement of elastic fibers and laminae is gradually lost over time, and thinning; splitting; fraying and fragmentation are observed. The degeneration of elastic fibers is associated with an increase in collagenous material and in ground substance, often accompanied by calcium deposition in ground substance and in degenerate elastic fibers [38,39]. By contrast, muscular arteries, like the brachial and radial arteries, do not stiffen with aging in normal individuals [40–42]. The present results suggest that the stiffening process induced by IBD and associated inflammation differs from that of aging (Fig. 2, Panel a).

In clinical practice, measuring carotid–radial stiffness in IBD may help to estimate the amount of damage induced by inflammation on the arterial system. Measuring carotid–femoral stiffness may help to better predict the cardiovascular risk in these patients. Indeed, arterial stiffness, which is increased in high cardiovascular risk populations such as in patients with chronic kidney disease, hypertension, diabetes, hypercholesterolemia and smoking [43–48] has a predictive value for cardiovascular events and all-cause mortality independent of classic cardiovascular risk factors in the general population and in patients at high cardiovascular risk [13–16]. The carotid–femoral PWV of patients with IBD enrolled in the present study, expressed according to the reference value project [49], was above the 75th percentile of the normal value reported in healthy people with comparable age and blood pressure levels [49]. This finding is consistent with the results of the present report and supports the hypothesis that the cardiovascular risk of patients with IBD is increased.

In the present study, central PP was increased in patients with IBD, very likely as a result of an increased aortic

stiffness, favouring the early return of wave reflection. Central blood pressure is now well accepted as the true load damaging target organs and being responsible for cardiovascular events.

The increased arterial stiffness detected in the present work in patients with IBD and in other chronic inflammatory disease [10,11] and the recent evidence of early atherosclerosis in IBD patients [2,3] support the role of inflammation in the pathogenesis of cardiovascular diseases. It is estimated that only one-half of the risk for cardiovascular disease is explained by conventional risk factors, including blood pressure. Indeed, newly individualized risk factors are not taken into account, particularly markers of small and large artery damage, including small artery remodelling, carotid intima–media thickening, endothelial dysfunction and arterial stiffening. All of these parameters have demonstrated their predictive value for cardiovascular events in high cardiovascular risk patients. Larger epidemiological studies are needed in patients with IBD to confirm the results of the present report and to further clarify whether the chronic inflammation and the arterial stiffening are associated with the cardiovascular risk of patients with nonconventional risk factors.

Methodological issues

The present study has several strengths. First, as age, sex, blood pressure, heart rate, weight, height and many cardiovascular risk factors are important determinants of arterial stiffness, we compared IBD patients to controls of similar age, sex ratio, brachial blood pressure, heart rate, weight and height, and excluded from this analysis IBD patients and controls with significant cardiovascular risks and open cardiovascular diseases. Second, this is the first study that has performed a comprehensive measurement of the elastic and muscular artery stiffness in patients with IBD. Third, we used the gold standard method for assessing arterial stiffness and measured carotid–femoral PWV with a high-fidelity applanation tonometer (SphygmoCor; AtCor Medical, Sydney, Australia) [12].

This study also has some limitations. The current study is a cross-sectional one; therefore, causation cannot be determined for any of the observed relationships. Nonetheless, the findings show strength of association, temporality, consistency, biological plausibility and gradient, coherence with previous studies and are analogous to the results reported in other population with chronic inflammation. These features make it probable that the findings reflect a biological phenomenon [50].

Our study population is small limiting the ability to generalize the findings to other clinical settings. A higher number of patients are needed to conclude with enough power, from subgroup analyses. Despite the small study population, post hoc power analysis revealed that the examined sample size provided adequate power for multiple regression analysis (94%) with a type 1 error rate less than 0.05.

Finally, the markers of inflammation CRP and erythrocyte sedimentation rate were evaluated only in patients with IBD and not in healthy controls. Therefore, a direct comparison of these two biomarkers in IBD patients and healthy controls was not available. However, our conclusion relates mainly to the clinical inflammatory state (IBD or not), rather than to the inflammation biomarkers.

In conclusion, the present study documents, for the first time, increased aortic and muscular artery stiffness in IBD patients and provides evidence demonstrating the potential contribution of inflammation to the arterial stiffening.

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All authors have contributed significantly to the submitted work. L.Z. contributed in the conception and design of the study; collection, analysis and interpretation of data; drafting of the manuscript and revising it for intellectual content.

M.C., S.R., M.D.G., L.D.P. and I.M. contributed mostly in the collection, analysis and interpretation of data.

S.L., P.B., G.I. and P.C. contributed mostly in interpretation of data and revising the manuscript for important intellectual work.

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Conflicts of interest

There are no conflicts of interest.

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Reviewer's Summary Evaluation

Reviewer 1

This study shows that pulse wave velocity (PWV) in the aortic trunk and in the upper limb is elevated in patients with inflammatory bowel disease (IBD). The paper presents novel results with an excellent discussion section, elucidating aspects of inflammation related to cardiovascular risk in this condition. The important significance of the results is that increased arterial stiffness, measured as PWV in IBD is independent of blood pressure. In addition, stiffness of muscular arteries shows a greater age dependency in IBD than in control subjects, although, overall, the age dependency is modest.