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Femoral Artery Ultrasound Examination: A New Role in Predicting Cardiovascular Risk

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Abstract

We compared intima–media thickness (IMT) and the prevalence of plaques in the common carotid artery (CCA) and common femoral artery (CFA) in apparently healthy participants. This multicenter study included 322 participants (59.9% female; age 20-78 years, mean 52.1 $\pm$ 15.3 years) who underwent Echo-color Doppler examination of the CCA and CFA bilaterally. Prevalence and composition of plaque were recorded. A significant ($P < .01$) difference between mean CCA-IMT and mean CFA-IMT was detected (0.70 vs 0.73 mm). Plaque prevalence was significantly higher in the CFA compared to the CCA (40.7% vs 30.4%). Atherosclerotic plaques were found in both CFA and CCA in 46% of the cases, solely in CFA in 38%, and in CCA alone in 17%. The observed difference in plaque prevalence was even greater when only fibrolipid isolated plaques were considered (CFA 39.4% vs CCA 22.1%). In a healthy general population, atherosclerotic plaques were present in the CFA but not in the CCA in over one-third of the cases. Further studies must confirm whether ultrasonography of the CFA might be introduced in the screening protocols for cardiovascular risk assessment.

Keywords

intima–media thickness, common carotid artery plaque, common femoral artery plaque, cardiovascular risk

Introduction

Atherosclerosis and consequent cardiovascular (CV) disease (CVD) represent the main cause of death in Europe, with wide differences in mortality rates between different countries.[1] In Italy, morbidity and mortality rates due to atherosclerotic disease remain high, despite the adoption of major prevention strategies, such as campaigns against smoking and excessive alcohol consumption, promotion of maintenance of healthy body weight, and participation in physical activity.[2]

Since major CV risk factors and the deriving risk equations are able to predict a substantial but limited proportion of CV events, the assessment of early vascular changes has gained increasing popularity in both prevention and clinical settings as a tool to improve CV risk stratification beyond traditional risk factors.[3-6] In addition to coronary arteries, carotid and lower extremity arteries are 2 districts where atherosclerotic lesions commonly occur. Carotid atherosclerotic lesions are regarded as an indicator of generalized atherosclerosis, and carotid intima–media thickness (IMT) is an established independent predictor of stroke and CVD.[7,8] The American College of Cardiology and American Heart Association guidelines on the assessment of CV risk gave a class IIa recommendation for carotid IMT ultrasound assessment in asymptomatic adults at intermediate risk of CVD.[9] Moreover, carotid IMT has been

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proven to correlate with future CV events[10] and in individuals undergoing revascularization procedures.[11]

The distance between lumen–intima and media–adventitia interfaces of peripheral arteries (carotid and femoral arteries) can be measured noninvasively by B-mode ultrasound. The presence and characterization of atherosclerotic plaques and the degree of stenosis can also be assessed.[12] Evaluation of the mean IMT of the peripheral large arteries is inexpensive, widely available, and easily reproducible.[13] In comparison with the carotid artery plaques, the association between femoral artery atherosclerosis and CVD has received less attention to date. Recently, femoral ultrasound examination has been shown to correlate with subclinical atherosclerosis,[14] to be associated with coronary artery calcium score (CACS),[15] and to be an independent predictor of future CV events.[16-20] For all, there is a growing interest on femoral ultrasound as an adjunctive tool to carotid examination for CV risk stratification, but no guidelines persist in recommending the use of femoral ultrasound as a screening tool.[21]

The aim of our multicenter study was to compare the mean carotid and femoral arteries IMT and the prevalence of atherosclerotic plaques in both territories in a sample of apparently healthy participants.

Materials and Methods

Study Population

This study is part of a large follow-up international twin study[22] conducted in Italy, Hungary, and United States to evaluate the role of genetic and environmental factors on atherosclerotic traits.[23-25]

Twins, previously enrolled in the Italian Twin Registry (ITR),[26] were invited by mail/e-mail to participate in the study. Participants older than 18 years and residents in Rome, Padua, Perugia, and Terni or their outskirts were invited to participate. None of the enrolled patients had a history of carotid surgery or pregnancy. A total of 322 healthy participants were recruited between March and December 2014 at the university hospitals located in the city of residence. All enrolled participants signed a written informed consent to participate in the study. Approval for the study was granted by the university ethics review board, and the study was performed conform to the declaration of Helsinki. All participants were assessed for the presence of CV risk factors, such as hypertension, diabetes, and smoking habits.[27,28]

Measurements

The entire measurement protocol was standardized among the 4 recruitment centers to avoid any potential intercenter bias. The same sonographer (A.D.T.) performed the measurements in Perugia, Terni, and Padua, whereas another sonographer (P.L.) performed the same protocol in Rome after careful training by ADT.

General risk factors assessment. Systolic blood pressure and diastolic blood pressure, mean arterial pressure (MAP), and heart rate were measured by TensioMed Arteriograph (Medexpert Ltd, Budapest, Hungary) on the dominant arm, with the participant lying in supine position after 10 minutes of rest. Height and weight were measured by OMRON BF500 device to calculate body mass index (BMI; kg/m^2). Relevant medical history and pharmacological treatment were self-reported by the participants. Participants were asked to fill in several extended questionnaires regarding sociodemographic characteristics, risk factors, and personal habits (smoking and physical activity).

Carotid and femoral arteries ultrasound protocol. All participants underwent peripheral arterial assessment by B-mode ultrasound using state-of-the-art commercially available high-resolution color-coded duplex sonography scanners (MyLab70, Esaote, Genova, Italy, Rome; Sonoscape S8, Perugia; Toshiba Aplio XG, Padua, Italy; Esaote MyLab60 in Terni, Italy), with high-frequency (12 MHz) linear probes.

The following vascular sites were examined in all participants:

- Supra-aortic vessels: Carotid arteries were examined bilaterally in both axial and transversal planes from the supraclavicular fossa to the submandibular angle, including common carotid artery (CCA), carotid bulb, and origin of both internal and external carotid arteries (ICA and ECA).
- Femoral district: the common femoral arteries (CFAs) were examined bilaterally, from their point of entry into the Scarpa triangle till the bifurcation in superficial and deep femoral arteries (SFA and DFA). The SFA was then examined from its origin till its point of entry into the Hunter canal, where it deepens and consequently IMT thickening or plaque identification and characterization are impaired.

Intima–media thickness and plaque were defined according to the Mannheim consensus.[29] In particular, IMT is defined as the distance from the leading edge of the lumen–intima interface to the leading edge of the media–adventitia interface. Intima–media thickness was measured on each investigated arterial segment online using calipers. To improve accuracy, at least 3 IMT measurements were taken in each segment and were averaged. In case of plaque presence, IMT value was measured in the adjacent plaque-free segment.

Atherosclerotic plaque was defined as an endoluminal protrusion of at least 1.5 mm or a >50% focal thickening of the IMT relative to the adjacent wall segment.[30] Plaque presence and its size on both transverse and longitudinal planes were recorded in each segment. Moreover, all observed plaques were classified according to their morphological characteristics/compositions[31,32] as:

- calcified if the plaque presented as hyperechogenic with echogenic shadow in its entire extension;
- fibrolipid (soft) if the plaque presented a hypoechogenic appearance in its entire extension; and
- mixed a combination of previous 2 types.

All the involved sonographers were specifically and carefully trained at the beginning of the study on all the different aspects of the shared screening protocol in order to reduce the potential bias of the 2 different operators.

Statistical Analysis

Descriptive analysis for investigated characteristics, including mean and standard deviation for continuous variables and percentage for categorical variables, was performed.

For the purpose of the study, Italian twin participants were analyzed as individuals rather than twin pairs, and statistical comparisons were performed within participants. Mean IMT in CCA (IMT CCA) and in CFA (IMT CFA) were calculated as the mean of IMT in right and left side for both segments. Moreover, intraindividual differences between mean IMT CFA and mean IMT CCA were calculated, and the mean of the differences was also estimated (Mean diff = mean IMT CFA − mean IMT CCA).

Carotid and femoral plaque was defined as the presence of at least 1 atherosclerotic plaque in any of the examined sections on the right and left side (internal, external, and common in carotid artery; superficial, deep, and common in femoral arteries).

Student *t* test for paired data was used to compare mean IMT values calculated in carotid and femoral arteries, and McNemar test was performed for comparison of plaque prevalence between the 2 arterial segments. Paired test is a powerful way to isolate the effect of the factor of interest from the effects of 1 or more variables possibly playing a role. In our sample, this approach allowed us to control for potentially confounding variables such as age, MAP, gender, clinical history, and drugs use.

We performed these analyses on the overall data set as well as on subsets of the data defined according to the presence of atherosclerotic risk factors. Moreover, plaque analysis was first carried out using the total sample and then replicated on a restricted sample characterized by the presence of only fibrolipid/mixed atherosclerotic plaques. Chi-square for trend test was used to test for linear trend across groups of age.

Twins were treated as independent observations in all analyses. In order to explore possible clustering effects, the analyses were also conducted using independent twins randomly selected 1 from each pair, and results were compared between the 2 approaches. All analyses were performed using Stata Software(version 11.2, StataCorp, College Station, Texas).

Results

The study population consisted of 322 participants: 129 (40.1%) participants were male and mean age at enrollment was 52.1 years (range 20-78 years). Demographic and clinical characteristics of the participants are shown in Table 1.

Table 1. Demographic and Clinical Participants Characteristics.

	n	Overall Sample, % or Mean ± SD
Age, years	322	52.1 ± 15.3
Gender, Male	129	40.06%
BMI, kg/m^2	322	25.50 ± 4.27
MAP, mm Hg	319	90.9 ± 12.9
Heart rate, /min	319	67 ± 10
Hypertension	67	21.27%
Diabetes	13	4.10%
Hypercholesterolemia	62	19.87%
Physical activity		
Moderate/vigorous	195	60.56%
Smoking habits		
Never-ex smoker	236	74.22%
Current smoker	82	25.79%
IMT		
Left common carotid IMT, mm	322	0.72 ± 0.22
Right common carotid IMT, mm	321	0.68 ± 0.20
Left common femoral IMT, mm	322	0.72 ± 0.25
Right common femoral IMT, mm	321	0.73 ± 0.26
Prevalence of Plaques		
Carotid plaque, left side	39	12.11%
Carotid plaque, right side	31	9.63%
Femoral plaque, left side	103	31.99%
Femoral plaque, right side	87	27.02%
Plaque composition		
Carotid plaque composition		
Calcified	21	21.43%
Fibrolipid or mixed	77	78.57%
Femoral Plaque composition		
Calcified	32	24.43%
Fibrolipid or mixed	99	75.57%

Abbreviations: SD, standard deviation; BMI, body mass index; MAP, mean arterial pressure; IMT, intima–media thickness.

Intima–Media Thickness

As reported in Table 2, mean IMT was 0.70 mm in the CCA and 0.73 mm in the CFA ($P = .0016$). The earlier difference was significant in men (mean 0.05 mm, $P = .0008$) but not in women (mean 0.02 mm, $P = .17$). Figure 1 shows mean carotid and femoral IMT distribution by age. As expected, IMT increased with age for both segments. Participants older than 41 years showed higher IMT values in the CFA compared to the CCA, while there were no differences between IMT CCA and IMT CFA values in participants younger than 40 years (mean IMT 0.531 mm and 0.532 mm, respectively). Moreover, the means of intraparticipant differences (Mean diff = IMT CFA − IMT CCA) were significantly different from 0 in the last 2 classes of age, 41 to 55 and ≥56 years.

Finally, participants were stratified by 4 atherosclerotic risk factors (hypercholesterolemia, present/absent; smoke habits, never smokers/ex or current smokers; BMI, normal weight/overweight or obese; MAP, above or below the median value detected in our sample, 90) and differences compared. Results were statistically significant for each comparison, except for BMI (Table 2).

Plaque Prevalence

About one-third (30.4%) of the sample had at least 1 plaque in the carotid artery (Table 2), whereas prevalence of plaques in CFAs was about 40% (McNemar test, $P = .0003$).

Table 2. Mean Intima–Media Thickness (IMT) Artery and Plaques Prevalence Overall and by Gender or Other Risk Factors.

	n	Mean IMT, Common Carotid Artery, mm	n	Mean IMT, Common Femoral Artery, mm	P^a	n	Prevalence of Carotid Plaques	n	Prevalence of Femoral Plaques	P^b
Total sample	321	0.70 ± 0.20[a]	321	0.73 ± 0.24[a]	.002	98	30.43%	131	40.68%	.0003
Gender										
Males	128	0.70 ± 0.21	128	0.75 ± 0.23	.0008	50	38.76%	60	46.51%	.10
Females	193	0.71 ± 0.24	193	0.69 ± 0.19	.17	48	24.87%	71	36.79%	.001
Hypercholesterolemia										
No	248	0.67 ± 0.19	247	0.69 ± 0.24	.01	61	24.60%	80	32.26%	.01
Yes	66	0.79 ± 0.20	67	0.84 ± 0.23	.05	33	49.25%	47	70.15%	.003
Smoking habits										
Never	165	0.67 ± 0.20	165	0.70 ± 0.22	.07	36	21.82%	55	33.33%	.005
Current and ex smoker	152	0.72 ± 0.20	152	0.76 ± 0.26	.008	58	37.91%	72	47.06%	.03
BMI										
Normal weight	151	0.62 ± 0.17	150	0.64 ± 0.23	.15	26	17.22%	44	29.14%	.001
Overweight/obese	170	0.76 ± 0.20	171	0.80 ± 0.23	.004	72	42.11%	87	50.88%	.04
MAP, mm Hg										
<90	166	0.61 ± 0.16	166	0.64 ± 0.23	.02	30	17.96%	46	27.54%	.004
≥90	152	0.79 ± 0.19	152	0.82 ± 0.22	.02	66	43.42%	84	55.26%	.01

Abbreviations: BMI, body mass index; MAP, mean arterial pressure.
[a]Paired *t* test, IMT carotid artery vs IMT femoral artery.
[b]McNemar test, prevalence of carotid plaque versus femoral plaque.

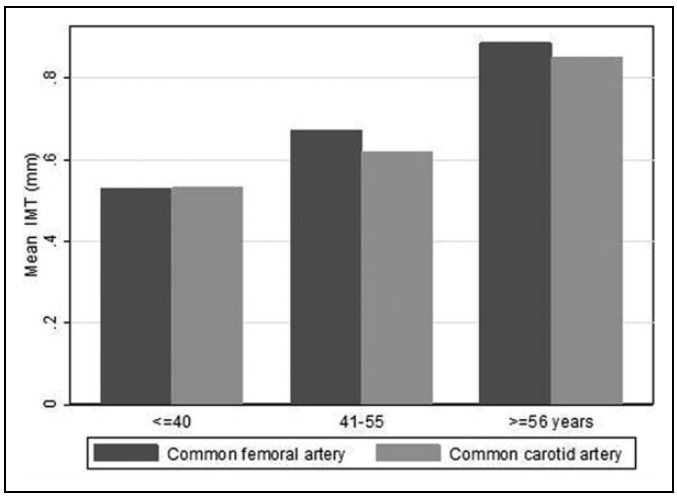

Figure 1. Mean intima–media thickness (IMT) in carotid and femoral arteries by age.

Prevalence of atherosclerotic plaques in both segments increased significantly by age (Chi square for trend $P < .01$), and the femoral site had higher prevalence in all age classes compared to carotid (CFA 10.5%, 31.0%, and 66.9% vs CCA 2.33%, 18.0%, and 57.4% in ≤40, 41-55 and ≥56 years, respectively). When our data were stratified, as described earlier, for the main risk factors, statistically significant differences in prevalence of plaques between carotid and femoral arteries were observed.

Participants were also classified taking into account the presence/absence and the site of the plaques simultaneously. Half of the sample had no plaques and, among participants with at least a plaque, 46% had a plaque in both segments. Prevalence of isolated femoral and carotid plaques was 38% and 17%, respectively. Distributions are reported in Figure 2A.

As shown in Table 1, most of the plaques had a fibrolipid or mixed composition (78.6% in the CCA and 75.6% in the CFA), and only few individuals showed calcified atherosclerotic plaques (about 20%). When the analysis was restricted to the participants with fibrolipid or mixed-composition plaques, as previously detected in the total sample, frequency of isolated plaques in the CFA (39%) was higher than in the CCA (22%). The prevalence of fibrolipid or mixed plaque in the CCA and/or CFA is shown in Figure 2B.

Results changed slightly only when the analyses were restricted to independent twins selected at random, 1 from each pair, indicating minor clustering effects. In particular, significant differences were detected between carotid and femoral IMT (paired *t* test $P = .03$) as well as between prevalence of plaques in the 2 arteries (McNemar test, $P = .002$).

Discussion

Our study demonstrated that mean IMT was significantly greater in the CFA than in the CCA in our healthy population (Figures 3 and 4). This difference, though relatively small in magnitude, needs to be carefully taken into account, as the reported CCA IMT values are in line with the reference CCA IMT values elaborated by large cohort studies (30, 32). Mean CFA IMT was higher in the subgroup of participants older than 41 years. Interestingly an isolated femoral plaque was found in over one-third of the investigated participants. These results suggest the hypothesis that early intima–media thickening at the common femoral site could represent a prompt marker of subclinical atherosclerosis. Therefore, especially considering the distribution of CVD by age in the general population[33] and

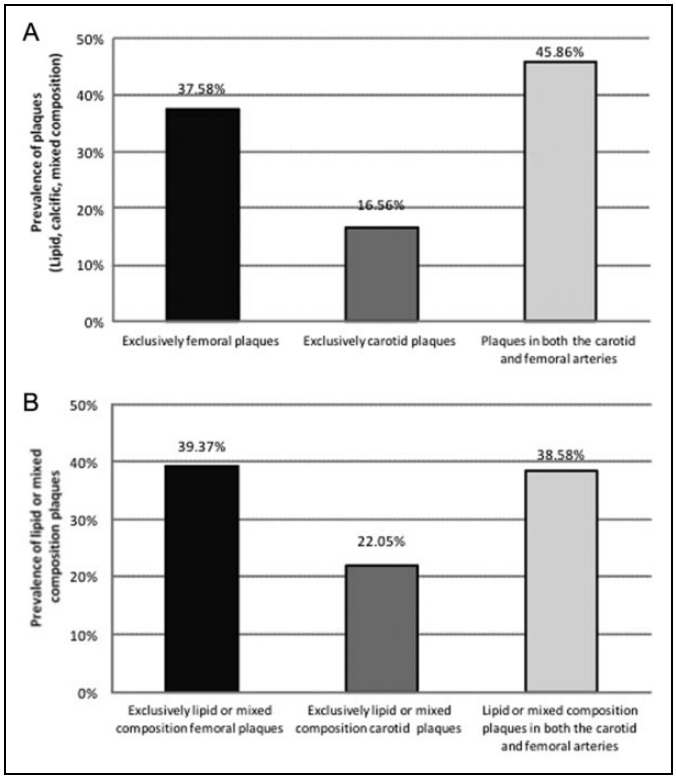

Figure 2. Prevalence of plaques in carotid and/or femoral arteries. All plaque compositions (A) and fibrolipid or mixed composition plaques (B).

the high prevalence of isolated femoral plaques in our sample, CFA IMT ultrasound assessment might gain a role in the evaluation of CV risk if further studies confirm our findings. More in detail, according to the current guidelines of the American College of Cardiology and American Heart Association on the assessment of CV risk, carotid IMT ultrasound assessment received a class IIa recommendation to be used in asymptomatic adults at intermediate risk of CVD.[9] Based on our results, the evaluation of CFA could be considered at least as an alternative option in the same population. Furthermore, with the aim to reliably assess the CV risk in patients, the high prevalence of isolated femoral plaque suggests that, in a certain percentage of cases, a subclinical atherosclerotic condition can be misdiagnosed in patients evaluated for carotid disease only. Other authors already suggested a major role of CFA ultrasound evaluation in the management of CVD. For instance, Khoury et al demonstrated that atherosclerotic plaques in CFA represented stronger predictors of disease than in CCA in a population of 120 patients with suspected coronary artery disease,[34] whereas Schmidt et al proved that CFA plaques can be predictive of CVD in middle-aged women.[35] Our results, derived from an outpatient asymptomatic population, suggest the idea that CFA ultrasound evaluation might be, in the near future, incorporated in the general guidelines for CVD risk stratification. The advantage of this incorporation may rely on the identification of a part of population otherwise missed if these patients are examined with carotid scan only.

Other relevant results of our study concern plaque composition, since most of the detected plaques had a fibrolipid or mixed structure. In addition, when analysis was restricted to participants with fibrolipid or mixed composition plaques, the frequency of isolated plaques in CFA was clearly higher than in CCA (39.4% vs 22.1%). Etiopathogenetic considerations arise from the latter observation, which may suggest at least a slight difference in the genesis of atherosclerotic plaques in CCA and CFA.[36] This hypothesis is even supported by differences between the distribution of atherosclerotic plaques in carotid and femoral sites already highlighted by previous authors. For example, Bossuyt et al observed a significant right–left difference in IMT of CFA but not of CCA and suggested a possible role of local geometry in the development of atherosclerosis[37]; however, this side difference has not been observed in our series. This idea is also strengthened by pathology and biochemical studies: Pathology studies demonstrated that atherosclerotic plaques sited in different segments of the arterial tree have commonalities in cell types, but their relative numbers and amount of connective tissue and lipids can vary considerably[36]; biochemical studies proved a different correlation between circulating lipoprotein and femoral plaques in comparison with carotid plaques.[38] Twin studies also reported a heritable component on carotid and femoral IMT, which makes a heterogeneous contribution to carotid IMT by segment.[24,39,40]

A potential role of CFA ultrasound evaluation in the general guidelines for CVD risk stratification has already been mentioned. Furthermore, the presented results on plaque prevalence and composition could have additional clinical impact on the management of patients with atherosclerosis[7,8]; for example, an earlier assessment of atherosclerotic plaques in CFA might lead to an earlier start of medical treatment (eg, statin therapy) in these patients. In addition, CFA IMT could be also used to assess treatment efficacy. Ibrahimi et al demonstrated that statin therapy is associated with a favorable increase in carotid plaque echogenicity; based on the high prevalence of fibrolipid plaques in CFA, we can speculate that the evaluation of CFA could represent an even better option to assess treatment effects in the same population.[41]

When carotid or femoral IMT and plaques prevalence were compared separately according to atherosclerotic risk factors, results were statistically significant for each comparison. These findings suggest that a combined US examination of the 2 districts can improve the detection of lesions in participants with or without hypercholesterolemia, smoke habit, overweight, or higher MAP values.

This study has limitations. One is related to the nonindependence of twin observations; however, the results of the analyses conducted on a subgroup of independent twins randomly selected 1 from each pair were comparable to those obtained on the total sample, and this suggested minor clustering effects. Furthermore, different ultrasound machines were used in the study centers. On the other hand, the strength of the study was the recruitment of a large population of healthy participants, whereas in previous studies on patients with atherosclerosis and femoral ultrasound had past history of CV events or were

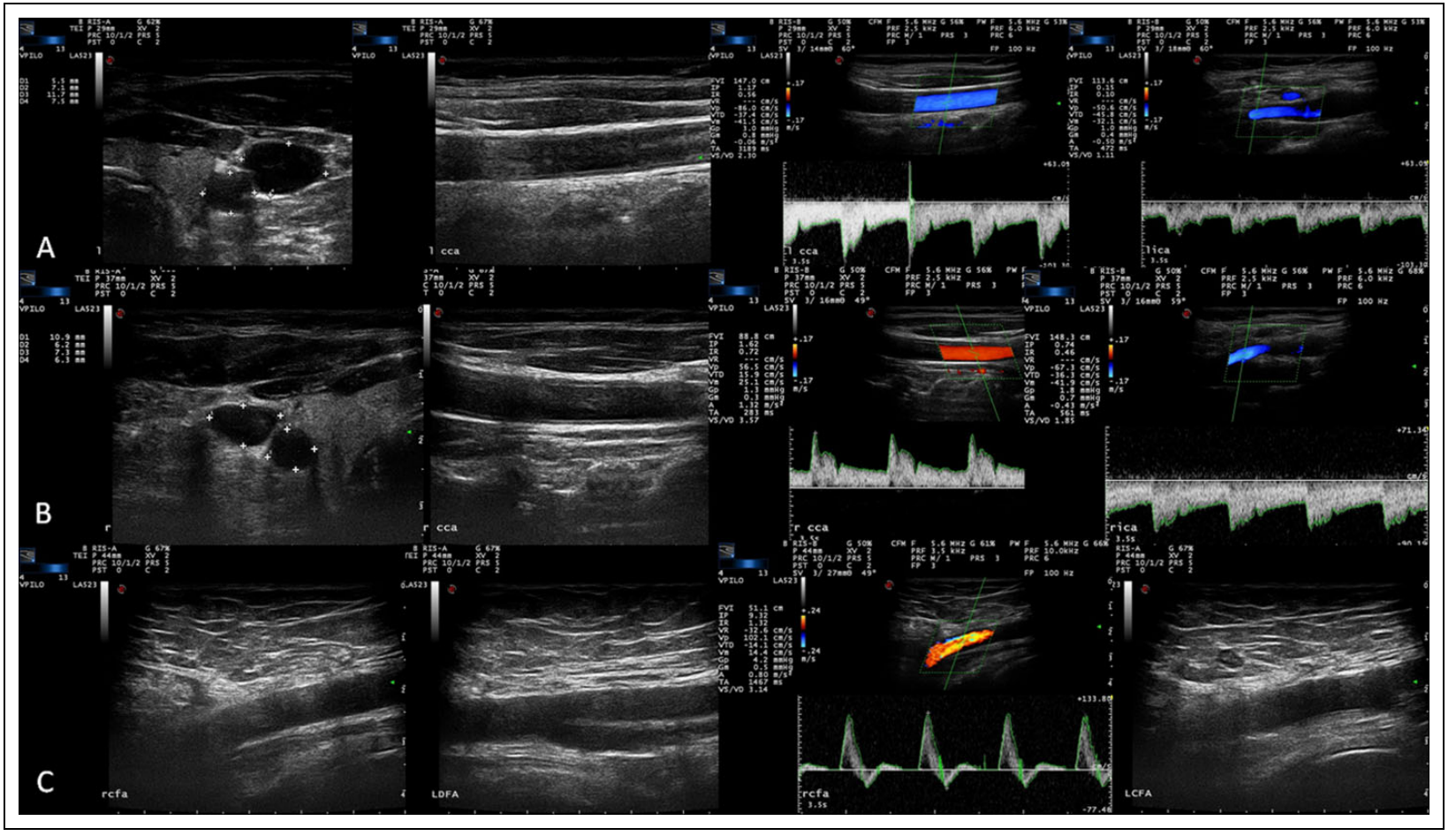

Figure 3. Forty-one-year-old male (Twin 1); echo-color Doppler examination showed no significant plaques in carotid (A and B) and femoral arteries of both sides (C).

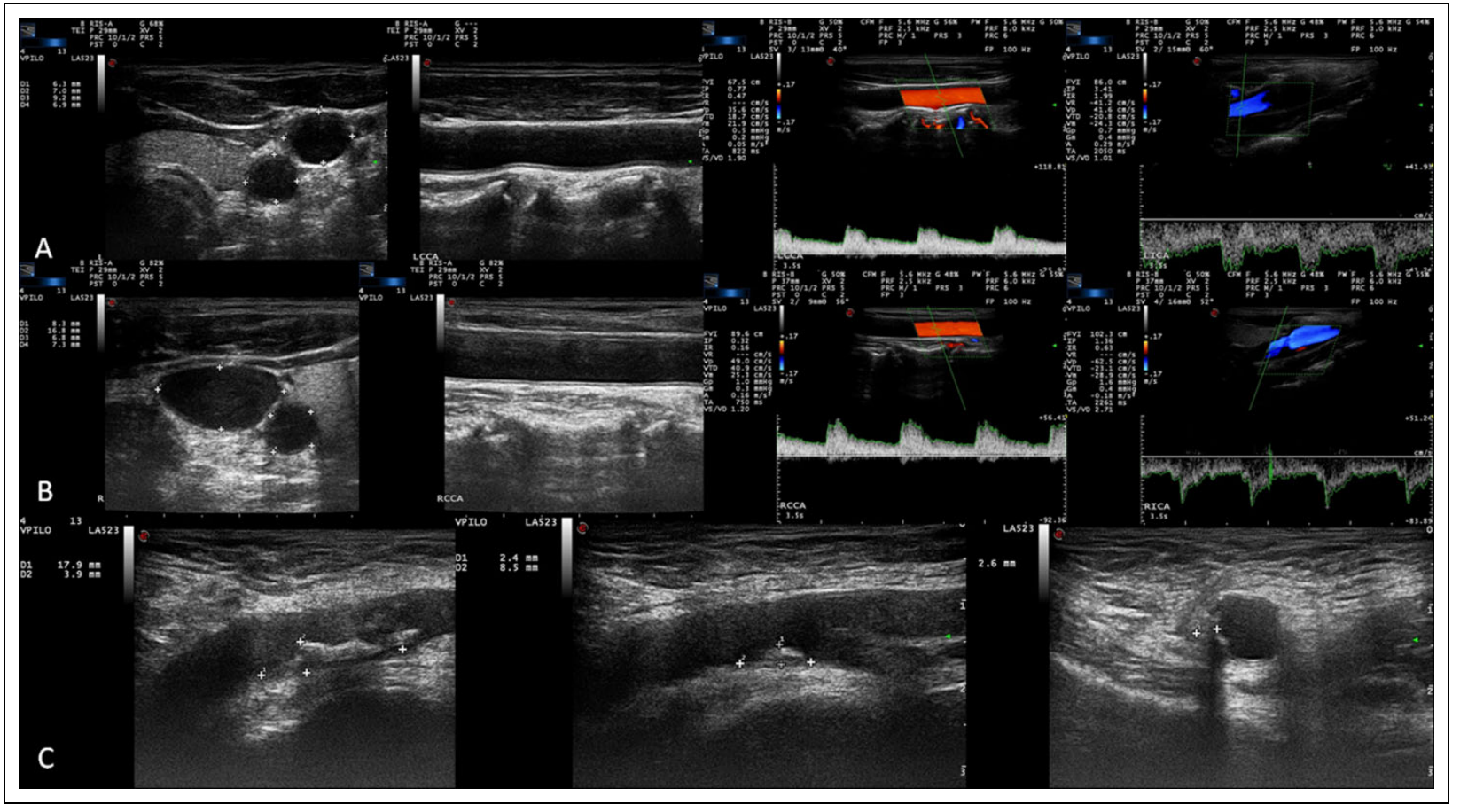

Figure 4. Forty-one-year-old male (Twin 2); echo-color Doppler examination showed no significant plaques in carotid arteries (A and B); in contrast, mixed plaques were detected in common femoral arteries (C).

already scheduled for endovascular treatment.[42,43] Moreover, our within-participants design has important advantages in terms of power and control of confounding.

In conclusion, our ultrasound study conducted on a general healthy population has identified more plaques in CFA than in CCA, with a high prevalence of isolated femoral plaque and fibrolipid composition. The CFA-IMT was significantly higher than CCA-IMT. If confirmed by future studies, these results suggest the potential use of CFA-IMT assessment as an early biomarker of atherosclerosis and the introduction of femoral artery ultrasound in the screening protocols for cardiovascular risk assessment.

Authors' Note

All authors (1) substantially contributed to conception and design, or acquisition of data, or analysis and interpretation of data; (2) contributed to drafting the article or revising it critically for important intellectual content; and (3) contributed to final approval of the version to be published.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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