# Fibrin clot properties in coronary artery ectatic disease: Pilot data from the CARE-ANEURYSM Study

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## INTRODUCTION

Coronary artery ectasias and aneurysms (CAEA), defined as (localized or diffused) coronary artery dilation(s) that exceed the adjacent segment diameter by at least 50%, are found in 2–7% of unselected patients undergoing coronary angiography for chronic or acute symptoms of myocardial ischemia [1]. CAEA may be associated with other vascular malformations [2]. Major adverse cardiac events are seen in up to 10% of CAEA patients per year [3] with acute myocardial infarction (AMI) as a frequent point of first CAEA diagnosis [1]. CAEA pathology is associated both with an increased AMI incidence [1] and recurrence [4]. Infarct-related artery CAEA is present in 5% of AMI patients [5]. Furthermore, in the majority of the AMI patients exhibiting CAEA, the thrombotic culprit lesion is located within CAEA [1]. In 50% of cases, CAEA is not accompanied by adjacent atherosclerotic coronary artery stenosis [6], suggesting that mechanisms other than atherosclerotic plaque rupture/erosion may contribute to the acute event of thrombosis and ischemia in CAEA. One such mechanism may involve increased inflammation different from that associated with atherosclerosis [7]. A "chronic prothrombotic state" has also been suggested to contribute to AMI risk in CAEA patients [1, 4, 8]; however, any mechanistic evidence to support this hypothesis is presently lacking.

CARE-ANURYSM is a prospective multicenter study of fibrin clot properties in consecutive CAEA patients (NCT05183373). In an initial sample of CARE-ANURYSM study patients, we evaluated fibrin clot properties in relation to clinical presentation and intravascular ultrasound (IVUS) imaging.

## METHODS

Fibrin clot properties, including clot permeability ($K_s$, reflecting an average pore size within the fibrin network [9]), and thrombin generation capacity (defined as plasma endogenous thrombin potential, ETP [9]) were evaluated in 10 consecutive CAEA patients presenting on an acute or elective basis. In AMI patients, at least 6 months had to pass from the AMI to blood sampling because the acute infarct pathology affects fibrin clot properties [10]. Active inflammatory diseases, renal disease, and active anticoagulation treatment were key exclusion criteria. Control data were obtained from 10 age- and sex-matched healthy control subjects. The protocol is available at ClinicalTrials.gov (NCT05183373).

In the present sample, coronary angiographic evaluation was supplemented with intravascular imaging employing virtual histology (VH-IVUS) [12] to visualize any accompanying atherosclerotic components and perform CAEA IVUS measurements. Scanning electron microscopy (SEM) analysis of plasma fibrin clots was performed in all study subjects and controls and was extended to the thrombi retrieved from the CAEA-culprit lesion in patients undergoing thrombectomy. The study was approved by the institutional Ethics Committee (no. 1072.6120.154.2021) and was conducted in accordance with the Declaration of Helsinki. All patients and control subjects provided written informed consent.

### Statistical analysis

Data were presented as numbers and proportions or medians and ranges (min-max), as appropriate. The Mann-Whitney U test was used to compare variables between the groups. *P*-values <0.05 were considered statistically significant.

## RESULTS AND DISCUSSION

Supplementary material, *Table S1* shows individual clinical and IVUS characteristics along with individual $K_s$ and ETP values. A median age of CAEA patients was 62 (28–78) years; 90% were male. The majority (70%) presented as AMI (mostly ST-segment elevation AMI). The CAEA diameter measured by IVUS was 6.13 (4.90–8.50) mm, exceeding the reference diameter 1.71-fold (1.57–2.32). A median CAEA lumen area was 29.46 (16.27–37.34) $mm^2$. With regard to the presence/absence of AMI as the clinical presentation and the presence/absence of angiographically significant (i.e. >50% luminal diameter stenosis) atherosclerosis, 4 types of CAEA manifestations were identified (Supplementary material, *Figure S1*). The CAEA culprit lesion of AMI manifesting as intraluminal thrombus located in CAEA, was evident in 85.7% of CAEA AMI patients. Of those, two-thirds demonstrated angiographic co-existence of CAD; this, in all cases, was confirmed by VH-IVUS (representative example in Figure 1I). The remaining one-third demonstrated evidence of CAEA thrombosis in the absence of atherosclerosis, confirmed by angiography or IVUS (representative example in Figure 1II). A scenario of particular interest involved CAEA elective presentation in the absence of concomitant CAD, as exemplified in Figure 1III where the SEM image of a fibrin clot is contrasted with a typical clot image from a healthy control and that from a CAD patient not exhibiting CAEA. Yet another scenario involved CAEA in association with stable coronary atherosclerotic disease (Supplementary material, *Figure S1*).

Supplementary Figure S2 shows individual data on fibrin clot properties in CAEA subjects and age- and gender-matched healthy controls. Overall, endogenous thrombin generation capacity was 2-fold greater in CAEA patients compared to controls (2245 [481–2703] vs. 1074 [891–1230] nM×min; *P* <0.001), which was in line with a pro-thrombotic clot phenotype.

Furthermore, CAEA patients, compared to healthy controls, showed a 50% reduction in clot permeability ($K_s$ median 4.16 [1.76–6.02] vs. 8.18 [5.68–13.04] $\times 10^{-9} cm^2$; *P* <0.001; Supplementary material, *Figure S2*), indicative of significantly denser fibrin clots.

CAEA-related infarcts are often associated with high-burden thrombus formation and a significantly lower likelihood of successful reperfusion [5, 12]. The latter might suggest a potential clot structure refractory to thrombolysis. On the other hand, however, sluggish coronary flow in association with coronary dilatation provides a pro-thrombotic milieu [13] that might, per se, underlie the increased likelihood of in-situ thrombus formation [1, 3, 4].

Apart from the issue of the clinical risk of AMI-associated death and typically large-scale myocardial tissue loss in CAEA patients, optimal revascularization may be difficult to achieve in these lesions for anatomic reasons. Challenges include unavailability of the large-diameter coronary stent ("large" coronary stents expand maximally to 6 mm) and stent sizing in vessel segments where the CAEA neighbors a "normal" low-diameter lumen ("step-up/step-down"), resulting in a substantial risk of stent under-expansion and malapposition [5]. To complicate matters further, the no-reflow phenomenon is highly prevalent in CAEA-associated AMI [12, 14], and recent multivariant analysis has identified CAEA as an independent predictor of adverse outcomes in primary percutaneous intervention [5]. It is not clear to what extent the markedly impaired post-intervention coronary and myocardial tissue flow results "just" from the large thrombus volume in these patients [12] or, potentially, from the contribution of a detrimental clot structure as suggested by our pilot analysis (Figure 1; Supplementary material, *Figure S2*).

Atherosclerotic coronary disease, similar to several other cardiovascular pathologies, is associated with formation of dense fibrin networks as manifested by low $K_s$ values [15]. Thus CAD presence in 50% of CAEA in this study sample might have contributed to overall abnormal fibrin clot properties exhibited by our CAEA patients. While our sample size was not sufficient to perform comparisons among the CAEA patients with versus without CAD accompanying the CAEA pathology, individual patient data demonstrate altered fibrin clot properties in the CAEA subjects without coronary atherosclerosis (Supplementary material, *Figure S2*). Thus, our findings provide some initial support for our hypothesis that the CAEA pathology might be associated with abnormal fibrin clot properties.

### Limitations

This is a pilot analysis of an initial sample of CAEA patients recruited in the CARE-ANEURYSM study. This sample size is not powered for further comparisons of interest, such as CAEA patients with vs. without a history of myocardial infarction, with vs. without coexisting CAD, or CAEA patients vs. those with aneurysmatic arterial disease in other territories (such as abdominal aortic aneurysm). Those, and other comparisons, will be performed in the larger-scale, multicenter study(ClinicalTrials.gov NCT05183373).

### Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

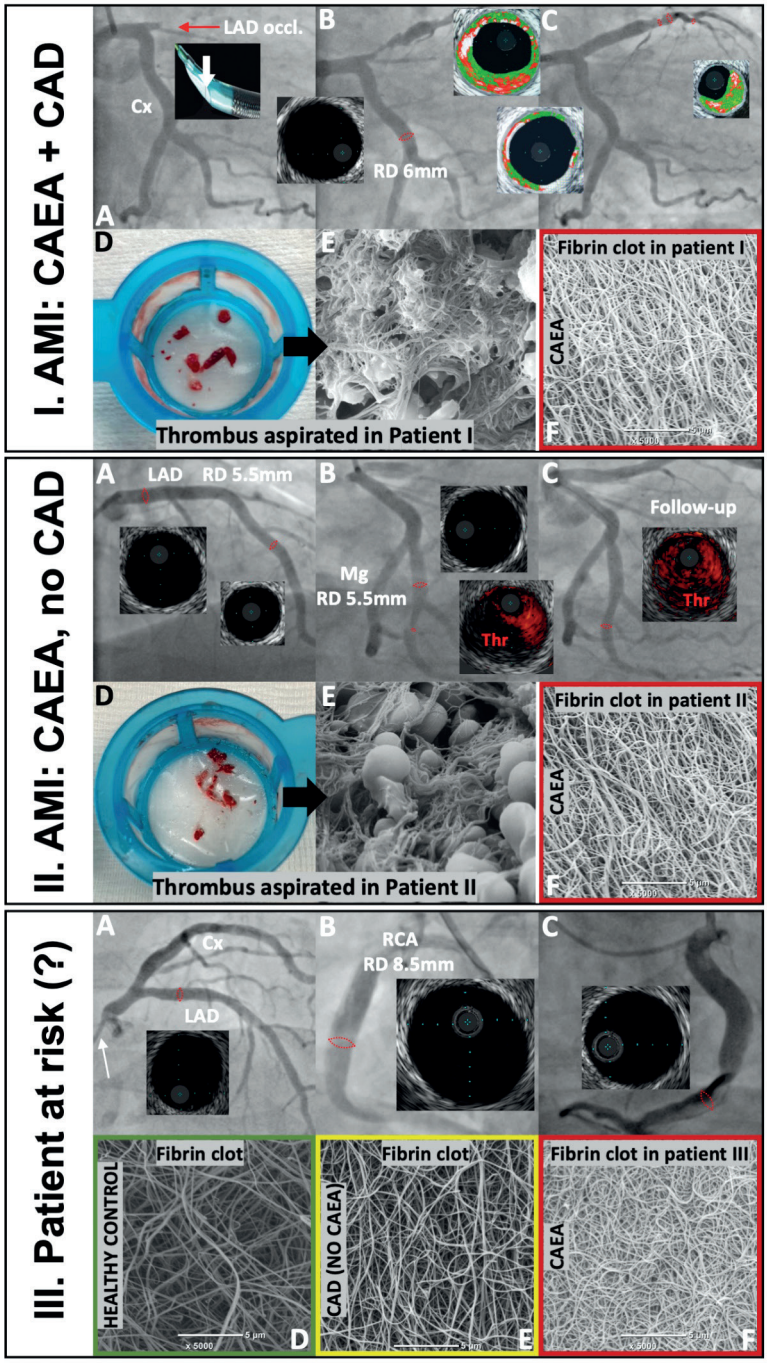


**Figure 1.** Coronary angiographic, intravascular ultrasound imaging, and scanning electron microscopic clot structure in different CAEA clinical presentations. **I.** CAEA patient with AMI and angiographically significant coronary atherosclerosis. A 44-year-old male was admitted with AMI due to proximal ectatic LAD occlusion. **A.** Left coronary artery: LAD occlusion (red arrow) and ectatic circumflex artery (Cx, angiographic reference diameter [RD] of 6 mm); inset shows a thrombus aspiration catheter (white arrow points to the aspiration port). **B**. Evacuation of the culprit lesion thrombus (cf., **D**) revealed LAD ectasia. **C.** Optimal angiographic outcome of culprit lesion revascularization with stent implantation. IVUS insets show the diameter (gray-scale IVUS) and virtual histology frames in key spots (note the presence of atherosclerotic lesions whose components are color-coded; red CAEA patients necrotic core, white — calcium, green — fibrous content, yellow — fibrofatty content [11]). **D.** The thrombus aspirated in this patient, further imaged with SEM (**E**), demonstrating a very dense fibrin fibers structure (note the presence of erythrocytes that are absent in **F**). **F.** SEM morphology of the plasma fibrin clot in this patient showing, consistent with **E**, a very dense structure of fibers (compare with **Figure 1IIID**). Thrombin generation potential and a functional measure of plasma clot fiber density ($K_s$) were evaluated in all patients and controls (see Supplementary material, *Figure S2*). **II.** CAEA patient presenting with AMI in the absence of coronary atherosclerosis. A 28-year-old male presented with AMI; the culprit thrombotic lesion was located in an ectatic marginal branch (Mg). **A.** Ectatic LAD (RD of 5.5 mm). **B**. Ectatic Cx and Mg (RD of 6 mm). Gray-scale IVUS images (insets) show vessel diameters measured by IVUS and demonstrate the absence of atherosclerosis. ChromaFlo IVUS images (insets) demonstrate an intraluminal thrombus (Thr) that was reduced after a week of intensive anti-thrombotic therapy including both anti-platelet agents (glycoprotein IIb/IIIa inhibitor, prasugrel) and anticoagulation (unfractionated heparin followed by low molecular weight heparin). **D**. The coronary culprit (thrombus) evacuated with thrombectomy in this patient. **E**. SEM morphology of the aspirated thrombus (note erythrocytes). **F**. SEM morphology of the plasma fibrin clot in this patient (note, again, a dense fibrin fiber structure — compare with **Figure 1IIID**). **III.** Patient with chronic coronary syndrome and CAEA in the absence of atherosclerosis. A 70-year-old male was electively evaluated for chronic stable angina. **A**. Left coronary artery with the ectatic LAD and Cx (observe the large diameter of the vessel in relation to the diagnostic catheter [white arrow] that is 2 mm in diameter). **B**. Ectatic right coronary artery (RCA, RD of 8.5 mm) that demonstrated a very slow flow (potential culprit site for another AMI, cf. ref. 12). **C**. IVUS visualized very large coronary vessel diameters in the absence of thrombus or atherosclerosis. **D**. Typical fibrin clot morphology in a healthy control (for comparison with the CAEA patients in **I F**, **II F**, and **III F** and with the CAD patient in the absence of CAEA in **III E**). **E**. Typical fibrin clot SEM morphology in a patient with established coronary atherosclerotic disease in the absence of CAEA (for comparison with the CAEA patients **IF**, **IIF**, and **IIIF** and with the healthy control in **IIID**). **F**. Fibrin clot SEM morphology in CAEA in the absence of any accompanying coronary atherosclerosis (material from Patient III). For individual and median functional clot properties see Supplementary material, *Figure S2*

Abbreviations: AMI, acute myocardial infarction; CAEA, coronary artery ectasias and aneurysms; Cx, circumflex artery; IVUS, intravascular ultrasound imaging; LAD, left anterior descending coronary artery; RCA, right coronary artery; SEM, scanning electron microscopy

## *Article information*

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