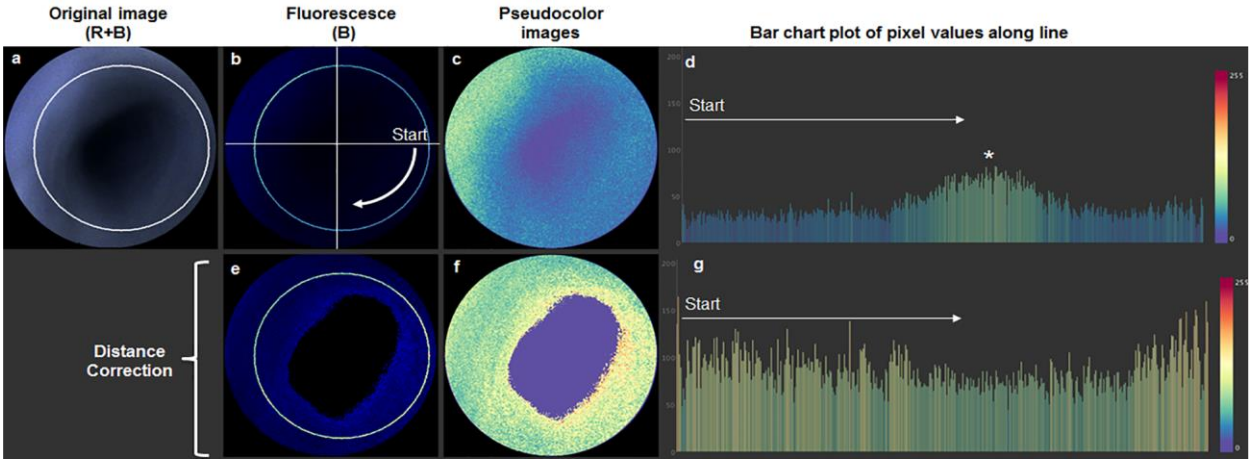
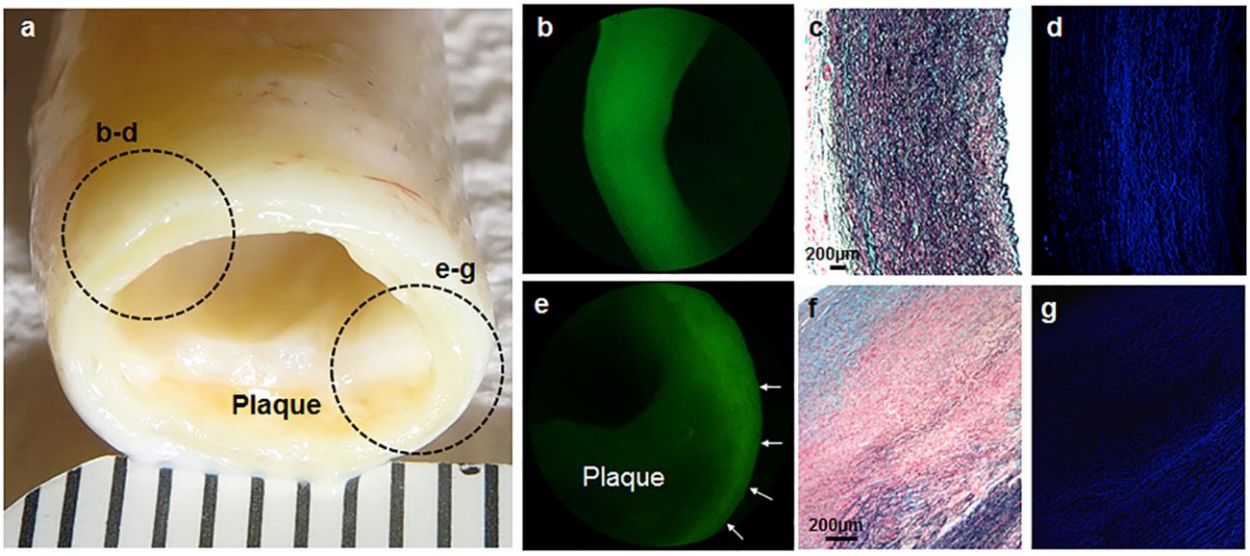
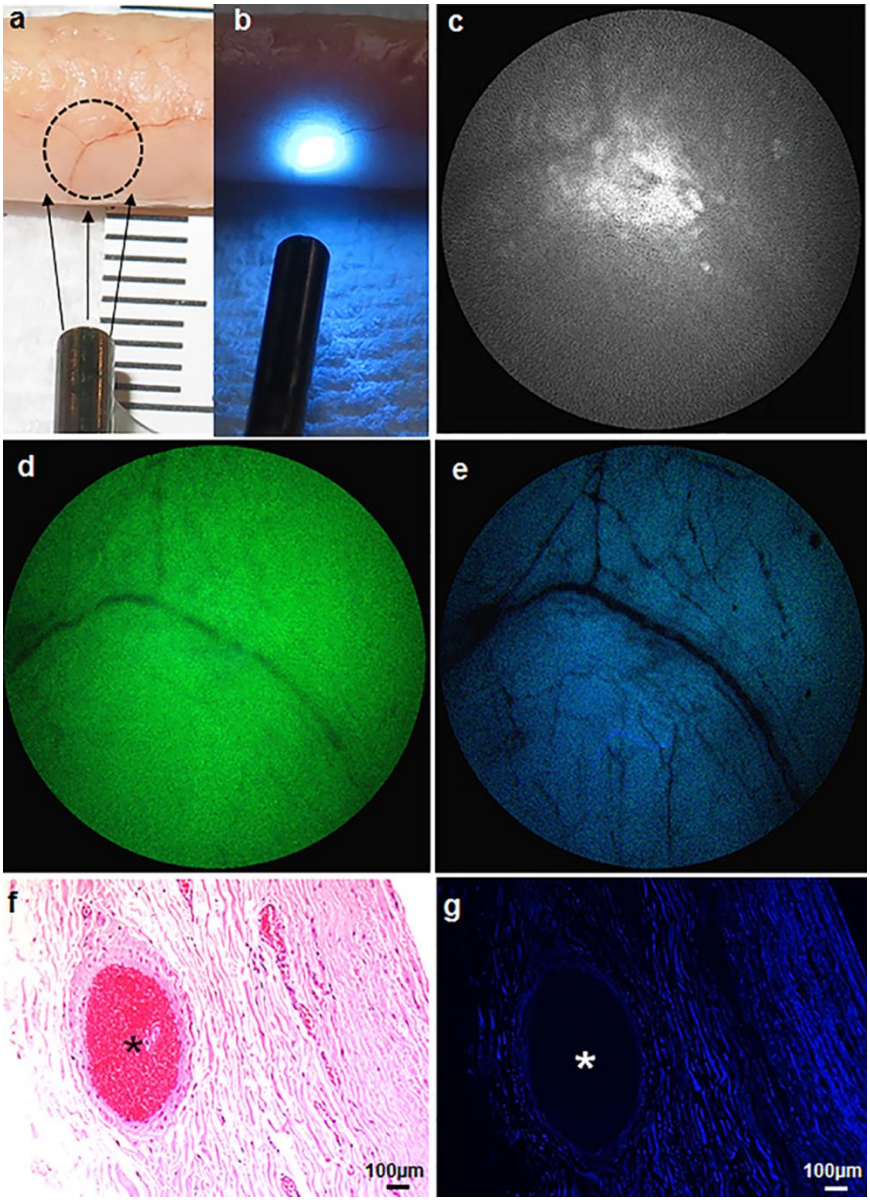


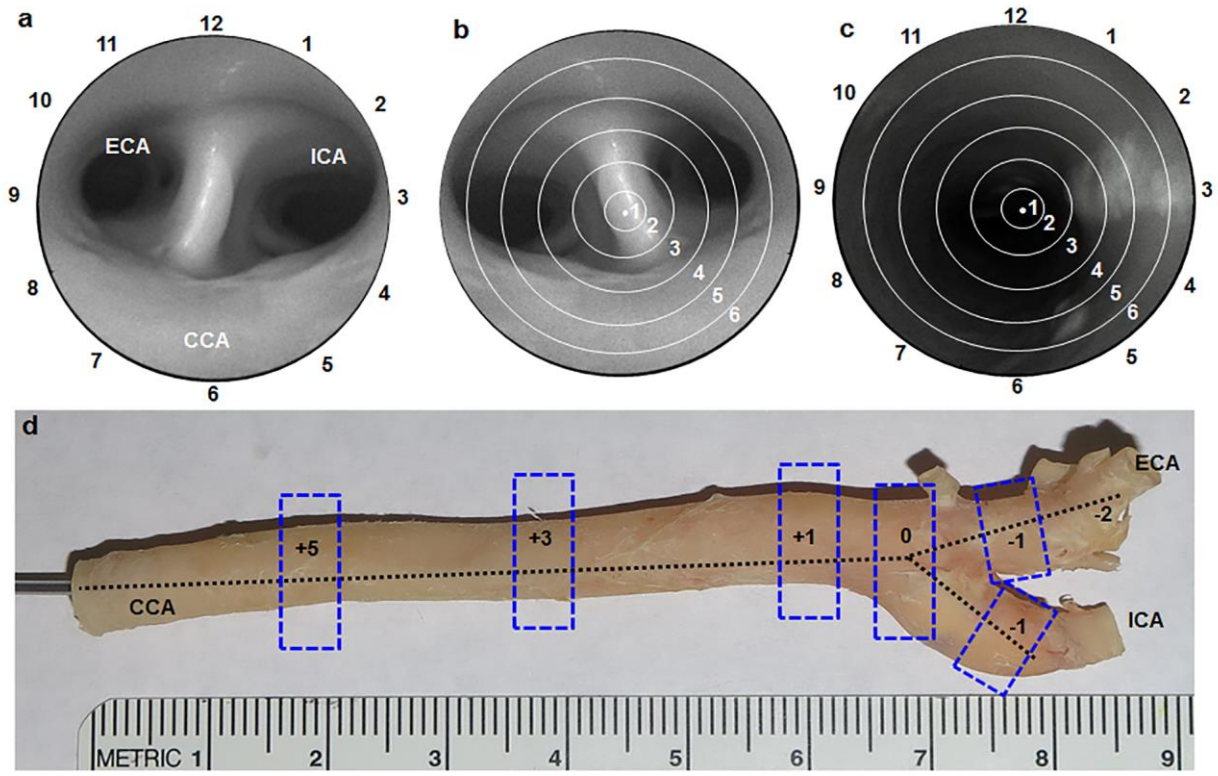
Supplementary Figure 1. Quantification of fluorescence signal after distance-compensation. Multimodal SFE image (**a**) obtained with merged backscattering from red laser or reflectance (R) and blue fluorescence (B), undergoes subtraction of reflectance to generate pure fluorescent images (**b**). Signal intensities of every pixel of the scanned field can be converted into pseudocolor images (**c** and **f**) and quantified. Fluorescent intensities of every pixel forming a line scan placed in image (**b**) are quantified in a clockwise fashion and plotted in a color-coded bar chart with a range of pixel values from 0 to 255 (**d**). Given the cylindrical nature of vessels and the intraluminal position of the SFE, the distance between the surface analyzed and the scope progressively increases from the periphery to the center of the field-of-view. In a similar fashion, vascular lumens are geometrically irregular secondary to intraluminal lesions and arterial bends, which translate into different distances from the surfaces analyzed to the SFE detector. To appropriately quantitate fluorescent signal intensities, images are corrected for distance using the method reported by Yang et al., 2013 (**e**). The bar chart resulting from plotting the color-coded pixel values of a line traced in (**e**) reveals a more homogeneous fluorescent signal after the distance-compensation algorithm is applied (**g**), with correction of the signal peak (asterisk) in (**d**) secondary to proximity artifact from vessel irregularity.



Supplementary Figure 2. Cross-section of carotid artery segment with fibroatheroma (a). (**b**) and (**e**) were obtained with the green laser of the SFE system (reflectance not included). (**c**) and (**f**) correspond to equivalent histological sections stained with Movat's pentachrome and reveal a relatively normal arterial wall and a Grade IV fibrous cap atheroma~~II intermediate plaque~~, respectively. (**d**) and (**g**) correspond to confocal microscopy images from unstained cuts consecutive to (**c**) and (**f**), respectively. Image (**b**) shows the typical homogeneous strong AF of a healthy vascular wall, largely formed by a TM (**c**). Confocal microscopy reveals very strong AF signal originating from elastin of the TM (**d**). Image (**e**) demonstrates outward displacement of the strongly fluorescent TM (arrows) by an expanding intimal fibroatheroma with characteristic low AF, which is confirmed by histological analysis (**f**). Confocal microscopy of consecutive arterial cross-section shows spectral contrast between low AF signal originating from the fibroatheroma facing the vascular lumen in comparison with intense AF signal from elastin in the TM (**g**).



Supplementary Figure 3. Visualization of stagnant hemoglobin within the *vasa vasorum* in the arterial wall with SFA. Note in (**a**) the tip of the SFE system is directed toward an artery located ≈8mm away, and the Y-shaped *vasa vasorum* (visible red, thin vascular structures). In (**b**), the lasers of the SFE were turned on and red reflectance (**c**), green (**d**), and blue (**e**) multimodal images were obtained. Note the faint dark gray cast of the *vasa vasorum* in red reflectance mode secondary to lower light backscattering from the hemoglobin within the *vasa vasorum* in comparison to the adventitia of the artery (**c**). SFE images after excitation with 424nm and 488nm lasers (red reflectance turned off) reveal the rich vascular arborization of the *vasa vasorum* as dark lines over a blue and green background AF from the healthy arterial wall (**d** and **e**). This phenomenon is most significant with the blue laser (424nm) due to the peak in light extinction coefficient of hemoglobin in that particular wavelength. Histological analysis of a cross-section of the vascular wall [H&E stain, (**f**)] reveals *vasa vasorum* in adventitia with abundant erythrocytes (asterisk), which exhibits negligible signal per confocal microscopy in the blue spectrum compared with the collagen and elastin of the arterial wall [asterisk, (**g**)].



Supplementary Figure 4. Endoluminal (a-c) and external (d) topography. Using a clock face localization system, horizontal and right/left orientation is given by assigning the origin of the ICA at hour 3 and the origin of the ECA at hour 9 (**a**). Then, equidistant rings are drawn from the center of the field to the periphery and numbered from 1 to 6 (**b**). By combining these systems (**c**), it is possible to identify one lesion at hour 3 extending from ring 3 to 6, and a second lesion between hours 5 and 6 involving rings 4 and 5. In (**d**), specimens with homogeneous endoluminal surfaces are serially sectioned at the level of the carotid bifurcation (0cm) and at +1cm, +3cm, and +5cm (from the carotid bifurcation toward the CCA), and at -1cm (from the carotid bifurcation toward the ECA and ICA). In order to externally locate endoluminal lesions, the SFE probe is introduced into an outer sheath labeled with a ruler and advanced until it reaches the end of the outer sheath (0cm). Knowledge of the depth of the sheath into the vessel allows appropriate selection of the segment of interest for histological analysis.

Supplementary Table 1: Target-to-background log ratios between different pathology categories.

Pathology Category	Estimate	Standard Error	P-value	Alpha	Lower	Upper
Pathologic intimal thickening	-0.9095	0.3083	0.0106	0.05	-1.5707	-0.2482
Atheroma	-0.9226	0.2815	0.0055	0.05	-1.5263	-0.3190
Initial xanthoma	-0.5665	0.2079	0.0164	0.05	-1.0124	-0.1207
Intraluminal thrombus	-1.9822	0.4875	0.0012	0.05	-3.0278	-0.9367
Ulcerated plaque	1.3360	0.3083	0.0007	0.05	0.6747	1.9973

Supplementary Table 2: Analysis of variance model (ANOVA) for log-transformed fluorescent target-to-background ratio comparison between different pathology diagnoses.

Pathology Diagnosis	Pathology Category	Estimate	Standard Error	P-value	Lower	Upper
Pathologic intimal thickening	Atheroma	0.01318	0.4175	0.9753	-0.8822	0.9086
Pathologic intimal thickening	Initial xanthoma	-0.3429	0.3718	0.3720	-1.1405	0.4546
Pathologic intimal thickening	Intraluminal thrombus	1.0728	0.5768	0.0840	-0.1644	2.3099
Pathologic intimal thickening	Ulcerated plaque	-2.2455	0.4360	**0.0001**	-3.1807	-1.3103
Atheroma	Initial xanthoma	-0.3561	0.3499	0.3261	-1.1066	0.3943
Atheroma	Intraluminal thrombus	1.0596	0.5629	0.0807	-0.1477	2.2669
Atheroma	Ulcerated plaque	-2.2587	0.4175	**<.0001**	-3.1540	-1.3633
Initial xanthoma	Intraluminal thrombus	1.4157	0.5300	0.0183	0.2790	2.5524
Initial xanthoma	Ulcerated plaque	-1.9025	0.3718	**0.0002**	-2.7001	-1.1050
Intraluminal thrombus	Ulcerated plaque	-3.3183	0.5768	**<.0001**	-4.5554	-2.0811

Supplementary Table 3. Test agreement between the endoscopic SFA diagnosis and pathology diagnosis.

Endoscopic Category	Pathology Category						
	Normal & Diffuse Intimal Thickening	**Initial Xanthoma**	**Pathological Intimal Thickening**	**Atheroma**	**Ulcerated Plaque**	**Intraluminal Thrombus**	**Total**
Normal	20	0	0	0	0	0	20
Early lesion	0	10	0	0	0	0	10
Intermediate lesion	0	1	5	0	0	0	6
Advanced lesion	0	0	0	6	0	0	6
Ulcerated plaque	0	0	0	0	5	0	5
Intraluminal thrombus	0	0	0	0	0	2	2
Total	20	11	5	6	5	2	49

The agreement (kappa) is 0.998; 95% CI 0.964-1.000.