XeCl Laser–Induced Fluorescence of Atherosclerotic Arteries
Spectral Similarities Between Lipid-Rich Lesions and Peroxidized Lipoproteins


Autofluorescence spectroscopy of arterial surfaces provides information about the distribution and composition of atherosclerotic plaques. The aim of the study was to determine whether accumulation of peroxidized lipoproteins in arterial walls, a process postulated to play a role in initiating atherosclerotic changes, can be demonstrated by fluorescence spectroscopy. XeCl excimer laser (308 nm)–induced fluorescence of human aortas containing early lipid-rich noncollagenous lesions exhibited marked red shifts and broadening of the fluorescence spectra compared with spectra from nonatherosclerotic aortas. Similar profiles were observed in spectra obtained from oxidatively modified low density lipoprotein but not native low density lipoprotein. In hypercholesterolemic rabbits with early foam cell lesions, spectral shifts resembled those of oxidized β-very low density lipoprotein, the major lipoprotein accumulating in arteries of rabbits fed cholesterol. XeCl laser–fluorescence spectroscopy of arterial surfaces may be useful for the identification of arteries accumulating modified lipoproteins (oxidized low density lipoprotein), a chemical change indicative of atherosclerosis in its early and probably reversible stages. (Circulation Research 1993;72:84–90)

Key Words • atherosclerosis • oxidized lipoprotein • fluorescence spectroscopy • XeCl laser

Arteries with atherosclerotic changes exhibit altered autofluorescence responses that provide information about the fluorophore-chromophore composition of the underlying lesions.1–13 Characterization of arterial tissue by fluorescence spectroscopy has been performed with various lasers including the argon ion (476.5 nm),1,3–7 XeCl (308 nm),8,11 XeF (351 nm),12 HeCd (325 nm),20 and N2 (337 nm) lasers. Advanced human atherosclerotic lesions as seen in unselected autopsy specimens are often highly collagenous and may contain surprisingly little lipid.14 The fluorescence properties of such lesions are strongly influenced by the matrix proteins forming the fibrous caps that cover advanced plaques.9 In contrast, early during atherogenesis, the subendothelial space is occupied by lipid-laden macrophages or foam cells, the major component of fatty streaks.15,16 According to current concepts, lipoproteins accumulating in foam cell lesions undergo peroxidative and hydrolytic modifications.17–22 It has been suggested that these lipoprotein modifications play an important role in attracting circulating monocytes and transforming them into lipid-laden foam cells.17

In this report, we have tested the hypothesis that lipoprotein peroxidation products in early atheromatous lesions can be detected by fluorescence spectroscopy. Experiments were performed using an XeCl laser because its wavelength (308 nm) permits excitation and detection of fluorophores commonly contained in tissues and because near ultraviolet light can be delivered through flexible optical fibers adaptable to cardiovascular catheterization techniques.

Materials and Methods

Laser Fluorimeter

A XeCl excimer laser (model LPX-600, Lambda-Physik, Germany) producing 60-nsec pulses of 308-nm light was used to elicit fluorescence spectra from arterial surfaces exposed to air or from lipoprotein solutions contained in high-purity quartz cells (Figure 1). XeCl laser fluence did not exceed 10−2 J/cm² to avoid changes in tissue autofluorescence due to laser irradiation.23 To minimize intraexperimental lipoprotein peroxidation, the cells were hermetically sealed under a nitrogen atmosphere.

The irradiated region of the sample was approximately 1 mm in diameter, a compromise between spatial selectivity and detectability of fluorescence emission. The emitted fluorescence was collected with fused silica...
optical fibers (Diaguide, Fort Lee, N.J.) with a core diameter not exceeding \( \frac{1}{10} \) that of the irradiated area in order to avoid shadowing of the target under irradiation. The end of the optical fiber was positioned perpendicular to the target surface, and its tip was precisely centered above the target at a distance equal to the length of the excitation beam diameter. These precautions minimize fluorescence distortion due to scattering and reabsorption within the tissue. 24 Collected fluorescence was transmitted through a fiberoptic system to a spectrometer coupled to a gated multichannel spectral analyzer (model OMA III, EG&G Princeton Applied Research, Princeton, N.J.). Fluorescence was induced by a single laser pulse and recorded during a 20-nsec gate positioned at the maximum amplitude of the fluorescence pulse.

Before each experiment, spectral calibration was performed using a mercury lamp (model EU-700-91, Heath Corp.) and a multiline argon ion laser (model 2016, Spectra-Physics Inc., California). The linear amplitude response range of the charge-coupled device array detector within the entire fluorescence spectrum was measured with the multiline argon ion laser (model 2016, Spectra Physics), the He-Ne laser (model 102-4, Uniphase, Sunnyvale, Calif.), and a set of neutral-density glass filters with known transmittance.

A high reflectance (99%) mirror (308 FR-1D-FL, ARC Corp., Acton, Mass.) was placed in front of the spectrometer entrance slit to suppress 308-nm back scatter from the sample. To improve the signal-to-noise ratio, at least four (average, seven) fluorescence spectra were obtained from each target site. Profiles of the spectra were numerically smoothed by using a narrow interval procedure. Smoothed spectra from different arteries and different arterial locations were compared by superimposing them. To facilitate comparison of the spectra, they were normalized with respect to integrated fluorescence intensity.

**Studies With Human Lipoproteins and Arteries**

Human lipoproteins (six samples) were fractionated by ultracentrifugation of pooled plasma collected in EDTA (1 ml/g) as previously described. 25 The lipoproteins were dialyzed against phosphate-buffered saline containing 0.01% EDTA. Protein in the samples was determined by the Lowry method using serum bovine albumin as a standard. 26 Oxidative modification of the low density lipoprotein (LDL) fraction (density, 1.019–1.063 g/ml) was performed by exposing native LDL for 24 hours to cultured rabbit endothelial cells equilibrated with serum-free F10 medium. 28 Samples of native LDL serving as control were subjected to incubations in F10 medium containing no cells. All LDL samples were resoluted by ultracentrifugation. The extent of lipoprotein modification was assessed by measurements of thiobarbituric acid–reactive substances and electrophoretic mobility as previously reported. 25

Human aorta samples were obtained at postmortem examination from 19 patients within 6 hours after death. The wide age range of the donors (10–73 years) ensured the collection of specimens with or without atherosclerosis of varying severity. 27 All samples were examined rapidly after excision to avoid artifacts resulting from prolonged storage. Throughout the experiments, the specimens were superfused with saline (21°C) to avoid tissue desiccation. Six to 10 samples, approximately 1 cm in size, were cut out from each aorta at sites thought to contain no atherosclerotic changes, fatty lesions (fatty streaks), or advanced fibrous plaques. Areas selected for spectroscopic study were marked with india ink and subsequently excised for histological examination. 6 Frozen serial 5-mm-thick sections were made through the centers of the irradiation sites with a diamond cutter, stained with a single batch of oil red O, and photgraphed. The sections were then fixed in 10% formalin, stained with Masson's trichrome (hematoxylin, fuchsin, and light green stains), and rephotographed. The photomicrographs were evaluated by two blinded independent observers and categorized according to the Stary classification of atherosclerotic plaques. 15

Sections exhibiting no changes or minimal changes including varying degrees of intimal thickening were called nonatherosclerotic (normal zones, Stary lesion type I). Fatty streaks (early lesions) corresponded to lesions containing layers of macrophages (foam cells) and extracellular lipid particles (Stary lesion type II). These lesions contained, by definition, no stainable collagen deposits. Samples exhibiting such lesions were obtained from the aorta of one child and four adults. Advanced atheromas represented lesions collected from middle-aged patients (56–73 years old) with either fibrolipid plaques (Stary lesion type IV) or purely fibrous (collagenous) plaques (Stary lesion type V). In our context, the term fibrous plaque (Stary lesion type V) was used when irradiation sites of the superficial intima (1-mm-thick subendothelial layer) contained a collagenous cap free of stainable lipid. In contrast, when irradiation sites contained, in addition to collagen, any stainable lipid, the lesions were called fibrofatty (Stary...
lesion type IV). Histological categorization and spectral analysis were performed independently (blind studies). The data were compared only after completion of all analytical procedures.

**Studies With Lipoproteins and Arteries From Rabbits With and Without Hypercholesterolemia**

Relations between spectroscopic characteristics of plasma lipoproteins and alteration in arterial autofluorescence were further evaluated in rabbits. Male albino New Zealand rabbits weighing 2.5–3 kg were placed on standard chow or on 1% rabbit cholesterol pellets as previously described. After a 10-week dietary period, plasma total cholesterol measured by the cholesterol oxidase method averaged 1.2±0.2 (mean±SEM) and 31.1±9.0 mM in control rabbits (n=6) and cholesterol-fed rabbits (n=6), respectively. Plasma was fractionated as described for human samples. The major cholesterol-carrying lipoprotein fraction in cholesterol-fed rabbits is recovered at a density of <1.006 g/ml (β-very low density lipoprotein [β-VLDL]). Samples of β-VLDL were oxidized by incubation with endothelial cells. Spectroscopic evaluation of rabbit aortas and native or oxidized rabbit lipoproteins (β-VLDL) were performed as described above.

**Chemicals**

In some experiments, fluorescence spectra were obtained from L-tryptophan (No. T-0254, Sigma Chemical Co., St. Louis, Mo.), an amino acid contained in some matrix proteins but not in elastin. Additionally, spectra were acquired from crude preparations of elastin extracted from the aorta of two children by the procedure of Lansing et al. All chemicals were purchased from Sigma.

**Analysis of Spectra and Statistics**

Fourteen of 131 human samples examined by the blinded observers (histologists) were assigned to different Stary classes of atherosclerotic plaques. Data from these 14 samples were not included in the present analysis.

Sample groups selected according to their histological categories yielded, in general, similar fluorescence spectra (except Stary group IV), as assessed by gross fluorescence band shapes. To assess variance of measured spectra in each histological category, two parameters were determined for each spectrum: 1) the position of the fluorescence maximum and 2) the fluorescence bandwidth at half-maximal amplitude (FWHM). Standard deviations of parameters 1 and 2 from the mean values for Stary categories I (no or minimal changes) and V (lipid-free fibrous caps) were very small (<4 nm). Slightly larger values (<10 nm) were obtained for Stary category II (fatty streaks). In contrast, for Stary category IV (mixed fibro-lipid plaques), standard deviations were large (>100 nm), reflecting the compositional variance of the lesions. Therefore, measured fluorescence spectra belonging to Stary categories I, II, and V were averaged, but for fibrofatty lesions, we report here only selected examples of fluorescence spectra.

The statistical significance of differences (p values) between mean values of fluorescence maximum position for Stary groups I, II, and V was evaluated by analysis of variance using the SAS/STAT statistics program. The generalized linear model using a multiple comparison test yielded p values for each pair of Stary categories I, II, and V. Values of p<0.01 were considered to represent significant intergroup differences.

Fluorescence spectra for rabbit aorta samples and different lipoprotein preparations were analyzed by the same statistical procedure. There were no disagreements between the independent observers in the categorization of rabbit aorta samples.

**Results**

**Human Samples**

Averaged fluorescence spectra from six human LDL pools before and after their oxidative modifications are shown in Figure 2. The native LDL profile exhibits a single fluorescence peak at approximately 340 nm (Figure 2, continuous line). Oxidative modification of LDL produces a prominent spectral shift toward the red, with a maximum at approximately 430 nm. Standard deviations of the position of fluorescence maxima from the mean value do not exceed 4 nm for native and 6 nm for oxidized LDL. In addition, there is a significant broadening of the spectrum, consistent with an overlap of several fluorescence bands (Figure 2, dashed line). The fluorescence bandwidths for native and oxidized LDL were 55±4 and 145±6 nm, respectively.

The increased fluorescence of oxidized LDL at visible wavelengths is associated with a change in the absorption spectrum. Differences between the average absorption spectra from six native and six oxidized LDL samples in the wavelength range 240–800 nm are illustrated in Figure 3. The absorption bands present in native samples at 450, 480, and 520 nm are absent after oxidative modification. Qualitative and quantitative differences between spectra from native and oxidized LDL very similar to those depicted in Figures 2 and 3 were

![Graph showing fluorescence profiles. The fluorescence profile of native (nonoxidized) human low density lipoprotein is indicated by a continuous line. There is a fluorescence maximum at approximately 340 nm with no appreciable additional features. The fluorescence profile of low density lipoprotein oxidized by incubation with endothelial cells is indicated by a dashed line. Compared with native low density lipoprotein, the spectrum exhibits a marked red shift. Additionally, there is a broadening of the spectrum, consistent with multiple fluorophores.](image-url)
observed in a total of six preparations from six different plasma pools.

Figure 4a (continuous line) shows an average fluorescence profile elicited from three samples of a 12-year-old child aorta. These samples had no structural signs of atherosclerosis, including an absence of foam cells and stainable extracellular lipid. The nonatherosclerotic intima exhibited an abundance of finely reticulated material known to represent proteoglycan ground substance (Stary type I lesion. The spectrum from this sample reveals a broad emission band with a fluorescence maximum at approximately 370 nm, smaller peaks at 382 nm, 390 nm, and 430 nm, and a broad shoulder extending into the yellow range. The FWHM value is approximately 105 nm. Virtually identical spectra were obtained from the aorta of a 10-year-old child and two young adults. The average spectrum from the juvenile aortas with minimal changes (Stary type I, 10 samples from four aortas) was very similar to that depicted by the continuous line in Figure 4a, except that its major maximum was shifted 4 nm toward longer wavelengths.

Figure 4a (dashed line) depicts an average fluorescence spectrum taken from an adult aorta containing abundant foam cells and numerous extracellular oil red O-positive particles and pronounced thickening of the aortic wall but no collagenous deposits (Stary lesion type II, nine lesions from seven aortas). Compared with the nonatherosclerotic aorta (continuous line), there is a broadening of the spectrum with a marked shift toward the red and a maximum occurring at approximately 430±9 nm. Lipid-rich lesions (Stary type II) collected from a total of five aortas yielded similar spectra with an FWHM value of 170±10 nm. The probability value for the significance of the difference in position of the fluorescence maximum between lipid-rich plaques versus nonatherosclerotic (normal) human aorta walls was 0.0007.

An average spectrum of three crude preparations of human aortic elastin is depicted in Figure 4b (continuous line). The broad spectral band extends from the ultraviolet to the yellow range (FWHM, 105±4 nm), with a maximum at 407±3 nm. Similar spectra have been obtained from elastin with the use of a HeCd laser. Compared with elastin, the fluorescence spectrum of the nonatherosclerotic aorta appears to be shifted toward shorter wavelengths. This may reflect nonelastin matrix proteins, such as glycosaminoglycans abundant in l-tryptophan (Figure 4b, dashed line), an amino acid not contained in elastin. The XeCl laser-induced fluorescence spectrum of tryptophan was characterized by a position of the maximum at 362±3 nm and a FWHM value of 65±3 nm.

Figure 5 shows an average fluorescence profile from fibrous caps and representative fluorescence spectra from mixed fibrofatty plaques. The average fluorescence spectrum for well-developed fibrous caps without stainable superficial lipid (Stary type V, 18 lesions from 12 aortas) is drawn with a continuous line. The spectrum is narrower than that of the nonatherosclerotic human aorta (Figure 4a, continuous line), lacking the broad shoulder in the yellow range (FWHM, 85±5 nm). The position of the maximum for the fibrous plaque fluorescence is at 382±4 nm. The spectrum of fibrous plaques resembles that of crude collagen. The probability values of the significance of the difference in the position of fluorescence maxima between fibrous plaques versus normal human aorta and between fibrous versus lipid-rich plaques were 0.0012 and 0.0016, respectively.

![Absorption spectra of native (continuous line) and oxidized (dashed line) low density lipoprotein in solution. Oxidative modification results in a loss of absorption bands in the 430-540 nm wavelength region.](http://circres.ahajournals.org/)

![Graph showing fluorescence spectrum from human aortas. The continuous line indicates the spectrum from the aortic surface of a 12-year-old child (Stary lesion type I, slight intimal thickening with ground substance accumulation but without microscopic signs of atherosclerosis). The dashed line indicates the spectrum from the aorta of a young adult at a site containing a noncollagenous lipid-rich lesion (Stary type II). Panel b: Graph showing spectrum from a crude preparation of human aortic elastin (continuous line) and from l-tryptophan in aqueous solution (dashed line).](http://circres.ahajournals.org/)

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Rabbit Samples

Compared with human LDL, oxidative modification of rabbit \( \beta \)-VLDL produced a noticeable but less prominent spectral change, a phenomenon that may reflect VLDL's decreased susceptibility to oxidation compared with LDL.\(^{19,20} \) Figure 6 (continuous line) shows the average spectrum of the \( \beta \)-VLDL fraction (d<1.006 g/ml) from the plasma of six normocholesterolemic rabbits. Figure 6 (long and short dashed lines) depicts average fluorescence profiles from six unoxidized and six oxidized \( \beta \)-VLDL samples prepared from the pooled plasma of six hypercholesterolemic rabbits. The rabbit lipoprotein spectra are asymmetrical, suggesting that more than one fluorophore contributed to the total fluorescence pattern. The spectrum of normocholesterolemic rabbit plasma exhibits a major peak at 410±5 nm and minor peaks at approximately 450 and 468 nm (Figure 6, continuous line). These minor peaks become the major emission maxima in unoxidized \( \beta \)-VLDL prepared from hypercholesterolemic rabbit plasma (Figure 6, long-dashed line).

Oxidation of \( \beta \)-VLDL produces a broadening of the spectrum, which is less marked than that observed with oxidation of human LDL. Oxidation changes the FWHM value from 86±4 to 100±8 nm, which broadens the fluorescence bandwidth, but only 14 nm. In contrast to the oxidation of human LDL, oxidative modification of rabbit \( \beta \)-VLDL shifts the fluorescence spectrum toward the blue with the appearance of new maxima at approximately 382±3 and 394±3 nm (Figure 6, short-dashed line).

Figure 7 (continuous line) depicts the average spectrum from the aortas of six rabbits without hypercholesterolemia. As opposed to the nonatherosclerotic human aorta with a well-developed intimal layer abundant in glycosaminoglycans, the native rabbit intima is extremely thin, with the internal elastic membrane in close apposition to the endothelial cell layer. The fluorescence spectrum has a bandwidth of 103±4 nm and shows a major fluorescence peak at 407±3 nm, a fluorescence signature characteristic of elastin (Figure 4a).\(^9 \)

Figure 7 (dashed line) depicts the average spectrum from the thoracic aortas of six cholesterol-fed rabbits at the site of an advanced foam cell lesion. The spectrum exhibits a major peak at 382±2 nm and lesser peaks at 394±2, 450±4, and 468±4 nm, features found in the spectrum of oxidized \( \beta \)-VLDL (Figure 6, short-dashed line). The general profile of fluorescence spectra and FWHM values for lipid-rich plaques in rabbits strongly
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![Graph showing fluorescence spectra from the aortic surface of a normcholesterolemic rabbit (continuous line) and from the aortic surface of a hypercholesterolemic rabbit at a site containing a multilayered foam cell lesion (short-dashed line). The spectrum from the diseased rabbit aorta has similarities with that from oxidized \( \beta \)-very low density lipoprotein (Figure 6, short-dashed line).](image)

**Figure 7.** Graph showing fluorescence spectra from the aortic surface of a normcholesterolemic rabbit (continuous line) and from the aortic surface of a hypercholesterolemic rabbit at a site containing a multilayered foam cell lesion (short-dashed line). The spectrum from the diseased rabbit aorta has similarities with that from oxidized \( \beta \)-very low density lipoprotein (Figure 6, short-dashed line).

 resembles that of the oxidized \( \beta \)-VLDL. Spectra from rabbit aortas occupied by foam cell lesions were very reproducible and were seen in all rabbits both at the level of the aortic arch and descending thoracic aorta. The probability value of the significance of the difference in position of fluorescence maxima between lipid plaques and normal rabbit aorta walls was 0.0011.

**Discussion**

The major finding of this study is that arteries undergoing early atherosclerotic changes exhibit an altered autofluorescence that may reflect the fluorescent properties of the lipoproteins accumulating in the tissue.

In the case of human atherosclerosis, lipoprotein retained in the arterial intima belongs predominantly to the LDL fraction,\(^{21,22}\) possibly because of its high binding affinity to intimal glycosaminoglycans.\(^{31}\) Owing to its abundance in polyunsaturated cholesterol esters, LDL is particularly susceptible to oxidation.\(^{19}\) It is of interest that several of the features observed in the spectra of oxidatively modified LDL, such as position of maximum, fluorescence bandwidth, and nonsymmetrical complicated profile, are also seen in the spectra from pure fatty lesions in human aorta.

The opposite oxidation shift of the fluorescence spectra of human LDL and rabbit \( \beta \)-VLDL is an interesting finding that may be explained on the basis of the different compositions of these two lipoproteins. Compared with LDL, \( \beta \)-VLDL is much less abundant in polyunsaturated cholesterol esters, and it contains apoproteins other than apoprotein B (apoproteins E and C). These differences may account for disparate oxidative modifications and may explain the opposite shifts.

The similarities of the fluorescence spectra for oxidized lipoproteins in solution and lipid-rich plaques in both rabbits and humans support the view that oxidized lipoproteins are important determinants of the fluorescence of lipid-rich atherosclerotic plaques.\(^{19,32,33}\)

The fluorescence properties of LDL have been ascribed to the tryptophan residues of apoprotein B\(_{100}\).\(^{19,32,33}\) Oxidative modification of LDL is known to alter amino acid residues in apoprotein B\(_{100}\). One important change involves lysine residues, which undergo covalent linkage with lipid peroxidation products.\(^{21,32,33}\)

It has been suggested that peroxidation-related changes in LDL autofluorescence reflect 4-hydroxynonenal–amino acid condensation products.\(^{33}\) It is important to note, however, that the abundance and state of oxidation of polyunsaturated fats might by themselves contribute to changes in lipoprotein fluorescence.\(^{32,34,35}\)

Whereas the autofluorescence of early lipid-rich lesions in humans and rabbits may reflect the fluorescence properties of the dominant lipoprotein accumulated in tissue, the autofluorescence of arteries containing no superficial lipid deposits may express mainly the fluorescence of matrix proteins directly underlying endothelial surfaces. In nonatherosclerotic arteries with a thin intima, the fluorescence may reflect the abundance of elastin, whereas in arteries with advanced lesions, collagen may become the dominant determinant.\(^9\)

The fluorescence spectrum of normal human aorta is not identical to that of elastin, although it displays some important features of elastin fluorescence, such as the long broad shoulder in the range from 450 to 550 nm. Although elastin contributes to the fluorescence of normal aorta, other fluorophores in the well-developed human aortic intima may be important. In contrast, in the rabbit aorta, where the intima is very thin with the internal elastic membrane located directly under the endothelial layer, the fluorescence spectrum is similar to that of elastin (compare continuous line profiles at Figures 4b and 7).

In the normal human aorta, the position of the fluorescence maximum differs from that of pure elastin (370 versus 407 nm), which probably reflects other tryptophan-containing matrix proteins in the subendothelial space. The similarity between fluorescence spectra of normal aorta and elastin reported by Laifer et al\(^9\) may have resulted from the use of a longer excitation wavelength (325 versus 308 nm in this study). The longer effective penetration depth of HeCd laser radiation may lead to the induction of fluorescence from deeper structures, including the inner elastic membrane.

Overall, our findings confirm earlier reports that fluorescence spectroscopy may be a useful tool to characterize the composition of atherosclerotic lesions.\(^1-13\)

Fluorescence profiles of normal aorta wall and various plaques excited by the laser pulse at 308 nm differ significantly.

Because of its ability to effectively excite numerous tissue fluorophores, the XeCl laser radiation at 308 nm may be particularly useful for diagnostic applications. Angioscopic detection of arterial tissue containing peroxidized lipoproteins might prove important, since they may signal arteries at risk for the development of advanced lesions. Lesions with dense collagen may have a limited potential for true regression (absolute rarefaction of collagen).\(^{36}\) Therefore, identification of atherosclerosis before dense collagenization has occurred may be important for the prevention of advanced disease and its inevitable complications. According to current concepts, atherosclerotic plaques at risk for thrombotic complications may contain abundant foam cells.\(^37\)

Therefore, the occurrence in proximity to fluorescence spectra indicative of fibrous and lipid-rich loci might
help in the detection of advanced plaques with inflammatory cellular components, lesion characteristics thought to be risk factors for rupture and thrombosis.

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