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Comparison of Lipid Deposition at Coronary Bifurcations Versus at Nonbifurcation Portions of Coronary Arteries as Determined by Near-Infrared Spectroscopy

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Abstract

Atherosclerosis has been shown to develop preferentially at sites of coronary bifurcation, yet culprit lesions resulting in ST-elevation myocardial infarction do not occur more frequently at these sites. We hypothesized that these findings can be explained by similarities in intracoronary lipid and that lipid and lipid core plaque would be found with similar frequency in coronary bifurcation and nonbifurcation segments. One hundred seventy bifurcations were identified, 156 of which had comparative nonbifurcation segments proximal and/or distal to the bifurcation. We compared lipid deposition at bifurcation and nonbifurcation segments in coronary arteries using near-infrared spectroscopy (NIRS), a novel method for the in vivo detection of coronary lipid. Any NIRS signal for the presence of lipid was found with similar frequency in bifurcation and nonbifurcation segments (79% vs 74%, $p = \text{NS}$). Lipid core burden index, a measure of total lipid quantity indexed to segment length, was similar across bifurcation segments as well as their proximal and distal controls (lipid core burden index 66.3 ± 106 , 67.1 ± 116 , and 66.6 ± 104 , $p = \text{NS}$). Lipid core plaque, identified as a high-intensity focal NIRS signal, was found in 21% of bifurcation segments, and 20% of distal nonbifurcation segments ($p = \text{NS}$). In conclusion,

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coronary bifurcations do not appear to have higher levels of intracoronary lipid or lipid core plaque than their comparative nonbifurcation regions.

If coronary bifurcations preferentially contained lipid core plaque (LCP), one would expect them to be the dominant site of plaque rupture and acute coronary syndromes.¹ One study of 385 patients presenting with ST-elevation myocardial infarctions arrived at this conclusion, reporting culprit lesions within 20 mm of a bifurcation in 79% of cases.² However, the effect of bifurcation induced shear stress, the presumed mechanism for increased plaque deposition, has been shown to dissipate within 3 mm of a side branch, suggesting that a number of these cases involved lesions outside of the influence of a bifurcation.³ In fact, culprit lesions were found within 10 mm of a bifurcation only 57% of the time. Fujii et al reported a similar finding using optical coherence tomography; these authors found lipid rich, thin-capped fibroatheromas in close proximity to a side branches in only 51% of cases.⁴ Thus, we hypothesized that despite the propensity to develop atherosclerosis at bifurcation segments, plaque lipid would not be found preferentially at bifurcations. Using near-infrared spectroscopy (NIRS), we compared the lipid composition of bifurcation versus nonbifurcation atherosclerosis. We hypothesized that intracoronary lipid and lipid-rich plaques would be found with similar distribution at coronary artery bifurcation and nonbifurcation coronary segments.

Methods

Lipid maps of 1 coronary arteries were obtained in 100 patients. Written informed consent as approved by the institutional review board was obtained before angiography. NIRS data were obtained using the Lipiscan catheter (InfraReDx, Burlington, Massachusetts) from patients undergoing coronary angiography. All data were submitted to the Chemometric Observation of LCP of Interest in Native Coronary Arteries Registry (COLOR), a repository of NIRS data maintained by the manufacturer of the catheter used for lipid assessment. Enrollment in COLOR was open to any nonpregnant patient aged over 18 years in whom a native coronary artery was imaged with the device.

In each patient, the NIRS catheter was advanced over a coronary guidewire into at least 1 epicardial artery and then withdrawn at 0.5 mm/s by automated pullback device. The spectroscopic signal generates a chemogram image, a block chemogram, and a lipid core burden index (LCBI). The LCBI is a measure of total lipid signal indexed to the length of an arterial segment. The block chemogram is an assessment for focal lipid-rich plaque within 2-mm blocks (see Figure 1). Each block is assessed for the presence of lipid, with a LCP being defined as a yellow chemogram signal, a signal characteristic previously shown to correlate closely with the presence of a lipid-rich plaque.^{5,6}

All scans were reviewed for the presence of major bifurcations marked by the operator at the time of image acquisition. For those with an identified side branch, we determined the LCBI and assessed for LCP in the 10-mm region surrounding the side branch. The LCBI and presence of LCP were also determined for a 10-mm segment proximal and distal to the bifurcation region. If a proximal or distal nonbifurcation segment overlapped with another bifurcation region, it was excluded.

Mean LCBI at bifurcation and nonbifurcation segments were compared, as were the percentage of segments containing LCP. In determining the effects of coronary side branches on LCBI, we had to account for significant zero-inflation (i.e., >20% of the LCBI measures had a value of 0). The nonzero LCBI measures were distributed log-normally.

A 2-part mixed-effects model was designed to handle zero-inflated data with repeated measures to model LCBI (SAS macro MIXCORR, SAS Institute Inc., Cary, North Carolina⁷). Using this method, we simultaneously fit a logistic regression model for proportion of non-zero LCBI measures for all participants and a linear regression for the log of the mean LCBI level among observations having LCBI values >0. Models were fit with and without correlated random effects using a backward selection procedure. All statistical analyses were conducting using SAS v9.2 (SAS Institute Inc.). Odds ratios were calculated to determine whether any demographic variables correlated with LCP deposition at bifurcation segments. Two-sample *t* tests were used to compare age and body mass index. We used chi-square tests and, when appropriate, Fisher's exact test to compare all categorical variables.

Results

The study population included 100 patients, 79 men and 21 women. Demographic and clinical information for all participants is shown in Table 1. The majority of patients were referred for catheterization due to angina (*n* = 62) or an acute myocardial infarction (*n* = 21), with the remainder for atypical chest pain, heart failure, posttransplant surveillance, preoperative evaluation, or silent ischemia (*n* = 17). Obstructive coronary artery disease was identified in 80% of patients at the time of heart catheterization.

Of the 170 bifurcations identified, 156 had adequate comparative regions proximal to (*n* = 89) and/or distal to (*n* = 135) the bifurcation. Any NIRS signal for the presence of lipid was found with similar frequency at coronary bifurcation (79%), proximal (78%), and distal nonbifurcation segments (69%; *p* = NS). There were no significant differences in total lipid signal as assessed by LCBI and no increase prevalence of LCP when comparing bifurcation, proximal, and distal segments (Figure 2).

When all patients were compared, no clinical predictors of lipid deposition as assessed by LCBI were found. Even when using our 2-part model to account for the large number of zeros (in which only patients found to have any lipid were further analyzed), there was no significant association with the probability of a nonzero LCBI measurement with bifurcation (point of interest vs proximal/distal), age, body mass index, gender, hypertension, hyperlipidemia, diabetes, coronary artery disease, or taking lipid-lowering medication.

The impact of demographic and historical factors on the presence of LCP is shown in Figure 3. In this multivariate model, neither the presence of a bifurcation nor any coronary artery disease risk factor correlated with an increased presence of LCP. Younger age was the only statistically significant association with LCP when age was analyzed as a continuous variable and each year younger in age was associated with an increased risk of finding plaque (odds ratio 0.97, confidence interval 0.94–0.99).

Discussion

This study demonstrates that lipid is found with similar frequency and amount in coronary bifurcation and non-bifurcation segments. Whether assessed as total lipid deposition or as the presence of focal, lipid-rich deposits, there was no demonstrable predisposition for lipid deposition at coronary bifurcations, regardless of the underlying cardiac risk factors.

The association between coronary bifurcations and the development atherosclerotic plaque has been shown at autopsy to occur even at a young age.^{8,9} The anatomy and pathology are thought to be linked by the blood flow alterations at the site of coronary side branches. Change in flow creates an area of low wall shear stress, bringing atherosclerotic debris into contact with the endothelial surface.¹⁰ At the same time, low shear stress induces changes in the endothelium, leading to increased low-density lipoprotein uptake and permeability.^{11–14}

In vivo evidence of the link between shear stress and atherosclerotic progression has been demonstrated with the use of IVUS^{15,16}, however, studies assessing plaque composition at coronary bifurcations have yielded conflicting results. Two studies have reported increased plaque volume and lipid-rich necrotic core in bifurcation compared with nonbifurcation regions, notably with some variability between proximal and distal bifurcations.^{17,18} In contrast, Toggweiler reported finding increased plaque burden but no increase in the presence of necrotic core in bifurcation segments.¹⁹

The present study is unique in that intracoronary lipid was directly assessed by NIRS. Because lipid has a distinct spectroscopic pattern,²⁰ NIRS is unaffected by intracoronary calcium, which is a commonly recognized limitation of ultrasound-based platforms such as virtual histology. Potentially due to the limitations of these mechanistic differences, virtual histology was reported to be unreliable in determining necrotic core in a porcine model and has shown a relatively poor correlation with the identification of LCP shown by NIRS.^{20,21}

There are several potential explanations as to why bifurcations were not found to be preferentially lipid rich in our study. First, atherosclerosis is a dynamic process, and plaque composition undoubtedly changes over time. If bifurcations are the earliest sites of atherosclerosis, as suggested in autopsy studies, these plaques may be the most mature by the time patients reach an age when coronary angiography is needed.⁹ In addition, there are other factors known to produce changes in wall shear stress, including coronary stenosis and vessel curvature,¹¹ which are not accounted for in our study. Finally, unmeasured factors independent of shear stress may have influenced the presence of lipid deposition.

Although multiple risk factors play a role in developing atherosclerosis, none in the present study were associated with an increased risk of identifying lipid-rich plaque. In fact, only younger age showed a correlation with lipid deposition. This finding may result from selection bias given that the need for coronary angiography at a younger age suggests more aggressive coronary artery disease.

Our study was limited in that only bifurcations marked during acquisition were available for review. Previous studies suggest a selective tendency for plaque deposition on the coronary surface opposite the bifurcation.¹⁹ Whether this was present in our patients could not be

assessed using the NIRS catheter. Additionally, because only a minority of patients studied presented with acute myocardial infarction, definitive comments regarding bifurcation plaque in this setting must remain speculative.

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Figure 1.

Lipiscan of a 70-mm segment of the left anterior descending artery with its major bifurcations. The *gray boxes* indicate the 10-mm segment surrounding 2 coronary bifurcations, where the bifurcation LCBI was calculated. Along the bottom is the block chemogram where *bright yellow* identifies a high-intensity lipid signal and the presence of an LCP.

Figure 2. Regional LCBI and percent of segments containing LCP in bifurcation, proximal and distal segments (*left, middle and right bars* respectively).

Figure 3. Odds ratios for the presence of one 2-mm block containing LCP within the 10-mm bifurcation, proximal, or distal segment. BMI = body mass index.

Table 1

Demographic characteristics of the study population (n = 100)

Characteristic	% [*]
Age (yrs)	62 ± 11
Body mass index (kg/m ²)	30 ± 6
Caucasian	83
African-American	15
Other race	2
Never smoker	32
Former smoker (quit >6 mos ago)	35
Current smoker	33
Diabetes mellitus	38
Hypertension	88
Hyperlipidemia	84
History of coronary heart disease	71

* Percent unless otherwise noted.