“Does imaging paint a sugar-coated picture of diabetic vessels?”

Plaque composition in diabetics by IVUS and CT angiography

Szilard Voros, MD, FACC

See related article, pp. 376–383

Type 2 diabetes mellitus (T2DM) and its common clinical precursor, the metabolic syndrome, have become a major epidemic in the developed world; the most common cause of morbidity and mortality in such patients is atherosclerotic cardiovascular disease.¹ The primary metabolic derangements in diabetes lead to cellular changes in the arterial vessel wall and these culminate in well-defined morphological changes (Figure 1), which may be detected by imaging modalities.

METABOLIC DERANGEMENTS IN T2DM

The sine qua non of T2DM is insulin resistance, which leads to hyperglycemia and hyperinsulinemia. These primary metabolic abnormalities lead to specific changes in lipoprotein metabolism, leading to the phenotype of “atherogenic dyslipidemia.”² Peripheral insulin resistance leads to elevated triglycerides. Elevated triglycerides then lead to an increase in apoprotein B (ApoB) concentrations, primarily in the very low density lipoprotein (VLDL) fraction. As cholesterol ester transfer protein (CETP) moves triglycerides from VLDL to low density lipoprotein (LDL) in exchange for cholesterol esters, LDL particles become smaller (small dense LDL; sdLDL). ApoB-containing particles are atherogenic; they are retained in the vessel wall due to their binding to proteoglycans. sdLDL particles are more atherogenic, since they more readily penetrate into the

sub-intima and they are more readily oxidized. In addition, due to similar mechanisms, high density lipoprotein (HDL) particles are also smaller in T2DM, further contributing to the phenotype of “atherogenic dyslipidemia” (Figure 1).

CELLULAR CHANGES IN T2DM

There has been considerable debate whether the cellular changes leading to atherosclerosis are primarily fueled by elevated glucose levels or indirectly by the atherogenic lipoproteins. Overall, it seems that both conditions need to be present for the accelerated atherosclerosis to occur, mostly through shared intracellular signaling mechanisms.³ Endothelial cells up-regulate cellular adhesion molecule expression through both mechanisms. Smooth muscle cell (SMC) proliferation is primarily mediated by hyperinsulinemia, through the uncoupling of the PI3/Akt and MAP-kinase pathways. Macrophages take up oxidized lipoproteins through scavenger receptor-A and CD-36 and eventually undergo apoptosis due to lipoprotein overload, contributing to the lipid-rich necrotic core (LRNC). Hyperglycemia, acting through an up-regulation of MMP-9 expression, facilitates plaque rupture and intra-plaque hemorrhage; this further increases the availability of free cholesterol from the cell membrane of the red blood cells, contributing to the LRNC. Detection of the LRNC is one of the most important tasks for imaging today.

T2DM AND VASCULAR CALCIFICATION

There is no direct evidence that hyperglycemia or hyperinsulinemia per se accelerate vascular calcification; rather, it seems that it is the acceleration of all the processes described above that fuels vascular and extra-vascular calcification. Once again, vascular calcium is a major target for imaging techniques.

MORPHOLOGICAL CHANGES OF THE VESSEL WALL

As a result of the metabolic and cellular processes, the vessel wall undergoes significant remodeling in

From the Center for Prevention, Wellness and Women's Heart Disease, Fuqua Heart Center of Atlanta, Piedmont Heart Institute, Atlanta, GA.

Reprint requests: Szilard Voros, MD, FACC, Center for Prevention, Wellness and Women's Heart Disease, Fuqua Heart Center of Atlanta, Piedmont Heart Institute, Suite 2035, 95 Collier Rd, NW, Atlanta, GA 30309; szilard.voros@piedmont.org.

J Nucl Cardiol 2009;16:339–44

1071-3581/\$34.00

Copyright © 2009 by the American Society of Nuclear Cardiology.

doi:10.1007/s12350-009-9069-x

Figure 1. Metabolic derangements, cellular responses and morphological and compositional changes in the arterial vessel wall in type 2 diabetes.

accordance with the Glagov phenomenon, leading to specific geometrical and compositional changes that can be detected by imaging modalities.⁴ With the deposition of lipoproteins, proliferation of SMC and the apoptosis of macrophages, initial growth of the plaque occurs in an outward fashion, as the external elastic lamina (EEL) stretches to accommodate plaque growth; this “outward” or “positive remodeling” assures that there is no luminal compromise in early atherosclerosis. Once plaque burden reaches approximately 40%, the EEL can stretch no longer and further plaque deposition results in progressive luminal stenosis.

GEOMETRY AND COMPOSITION OF THE DIABETIC VESSEL WALL BY HISTOPATHOLOGY

Histopathologic characteristics of diabetic coronary atherosclerosis have been elegantly elucidated, both in terms of geometrical and compositional characteristics.⁵

With regards to geometry, diabetic vessels have larger plaque burden and more “positive remodeling.” With regards to composition, diabetic plaques have larger LRNC and larger calcified area, but interestingly, not more thin-cap fibroatheromas (TCFA) (Table 1). There are also more healed ruptures in diabetics. Overall, therefore, the combination of metabolic derangements and cellular changes in T2DM leads to significant positive remodeling, larger plaque burden, more calcification and more LRNC; such changes can be readily detected by a variety of imaging methodologies.

TRADITIONAL IMAGING IN T2DM

In accordance with the principles described above, ultrasound-based measurements of the carotid intima-media thickness (CIMT) have demonstrated that vessel-wall thickening, a sign of increased plaque burden, could be shown in diabetics compared to non-diabetics (0.71-0.98 mm vs 0.66-0.85 mm).⁶

Computed tomography (CT)-based quantification of coronary arterial plaque burden has become an important tool in practice and in research as well. Standard non-contrast-enhanced CT scans are excellent for the quantification of coronary artery calcification (CAC), since calcium is readily detectable and quantifiable with this method. A clinically relevant measure of coronary calcified plaque (the “Agatston score”) takes into account both the total amount and the density of calcified plaques and has been shown to provide incremental prognostic information in asymptomatic subjects without previous coronary artery disease (CAD).^{6,7} Interestingly, our group has shown that while the lack of coronary calcification excludes obstructive CAD in asymptomatic subjects, significant stenoses are found in 8.2% of symptomatic patients with a zero CAC score.⁸ Large, population-based studies have compared the extent of coronary calcification in diabetics to those without diabetes and have shown significantly higher median CAC values in both genders in almost every age group, validating that imaging techniques can identify the histopathological changes known to occur in diabetic vascular disease.⁹ However, it is well-known that only a

Table 1. Comparison of geometrical and compositional plaque parameters based on histopathology, VH-IVUS and coronary CT angiography

	Calcium (%)	LRNC % (LD-NCP %)	Plaque burden (%)
Histopathology	12.1 ± 11.1	11.6 ± 8.4	N/A
VH-IVUS	6.4 ± 6.3	10.8 ± 5.9	48.7 ± 10.7
Coronary CTA *	35.6 ± 20.2	9.8 ± 6.6	57.2 ± 12.2

LRNC, Lipid-rich necrotic core; LD-NCP, low-density non-calcified plaque; CTA, computed tomography angiography.

*Unpublished, preliminary data.

small portion of the atherosclerotic plaque is composed of calcium; therefore, non-calcified components go undetected by non-contrast-enhanced CT techniques.

CORONARY PLAQUE IMAGING WITH CT ANGIOGRAPHY

The current role and challenges of contrast-enhanced CT coronary angiography have recently been reviewed in this journal.¹⁰ Briefly, coronary computed tomography angiography (CTA) has been validated for the detection and quantification of coronary stenoses, using invasive x-ray angiography as reference standard. In addition, however, coronary CTA now allows for the detection of coronary arterial plaques as well. Semi-quantitative methods of plaque characterization, similar to the method used in the present paper, have been validated before.¹¹ Briefly, for this approach, the coronary tree is divided into 14–16 segments based on a modified American Heart Association (AHA) scheme and each segment is visually scored for the presence of stenosis on a four-point scale (0 = none, 1 = mild, 2 = moderate and 3 = severe) and for the type of plaque (0 = none, 1 = calcified, 2 = non-calcified and 3 = mixed). However, data on more precise, strictly quantitative analysis of coronary plaque composition with coronary CTA are sparse.¹⁰

INTRAVASCULAR ULTRASOUND (IVUS) WITH TISSUE CHARACTERIZATION

IVUS has become the reference standard for quantifying atherosclerotic plaque geometrical parameters in the coronary arteries, such as plaque burden [percent atheroma volume (PAV) and remodeling index (RI)].^{10,12} Furthermore, signal generated from the radiofrequency backscatter data allows for tissue characterization and the generation of a color, parametric map of the wall identifying dense calcium (DC), fibrous tissue (FI), fibro-fatty tissue (FF) and the LRNC on a frame-by-frame basis [IVUS-virtual histology (VH-IVUS)].^{10,13} In addition, by integrating information along the long axis of the artery, more comprehensive classification, such as the identification of TCFA, has been introduced. To date, VH-IVUS remains the gold standard of coronary plaque characterization; one study has shown that even compositional changes can be detected by this technique with the use of atherosclerosis-modifying therapies.¹⁴

In this issue of the journal, Pundziute et al present an elegant study comparing vessel wall findings between diabetic and non-diabetic subjects, using both coronary CTA and VH-IVUS data. They assessed coronary arterial plaques in 60 patients, 19 with T2DM, with both

IVUS and coronary CTA. Consistent with the biology described above, they were able to confirm that, in general, diabetics had more extensive atherosclerosis, as shown by the increased number of any plaque in those with T2DM on coronary CTA (7.1 ± 3.2 vs 4.9 ± 3.2 ; $P = .02$). In addition to an increased number of plaques, there was more extensive plaque deposition and wall thickening as evidenced by a larger plaque burden on gray-scale IVUS (48.7 ± 10.7 vs 40.0 ± 12.1 ; $P = .003$). With regards to plaque composition, diabetics had more advanced coronary calcifications. This was seen both on CTA and VH-IVUS; on CTA, diabetics had more calcified plaque (52% vs 24%; $P < .001$) and less non-calcified plaque (17% vs 35%; $P < .001$). Interestingly, Agatston score was similar between the groups (282 [54–278] vs 85 [3–326]; $P = .09$). VH-IVUS showed consistent data with overall more dense calcium (6.4% vs 4.5%; $P = .02$). In addition, VH-IVUS revealed higher percentage of LRNC (10.8 ± 5.9 vs 8.6 ± 5.2 ; $P = .01$). Importantly, the number of VH-TCFA was similar between the groups (7% vs 10%; $P = .4$).

There are two fundamental issues that merit discussion with regards to this paper; first, issues related to the confirmation of the biology of diabetic atherosclerosis by imaging techniques and secondly, issues related to the imaging techniques themselves.

CONFIRMING THE BIOLOGY OF DIABETIC ATHEROSCLEROSIS

It is clear from histopathology that diabetics have accelerated atherosclerosis and both CTA and VH-IVUS confirmed this in the present study. Overall, a higher number of plaques were seen by CTA and more vessel wall thickening was seen by VH-IVUS, indicated by higher plaque burden. We are told by the authors that all patients had symptoms suspicious for ischemia. We are also told that of the 19 patients with diabetes, 13 had obstructive CAD (68%) and of the 41 patients without diabetes, 22 had obstructive CAD (54%). Furthermore, we are told that mean luminal narrowing by quantitative coronary angiography (QCA) was $33.8 \pm 13.4\%$. However, the authors did not present any data on minimal luminal area (MLA), or the correlation between CTA- and IVUS-derived MLA. While the authors presented mean lumen area, MLA should correlate with focal obstructive CAD better and would be a more meaningful analysis.

Imaging insights with regards to plaque composition are rather intriguing. Dense calcium by VH-IVUS was $6.4\% \pm 6.3\%$; in a histopathological study of diabetic patients with sudden death, the proportion of calcified matrix was $12.1\% \pm 11.1\%$ (Table 1).⁵ This

difference is likely due to a combination of more advanced disease in the histopathologic study (patients with sudden death) and due to the lower sensitivity of VH-IVUS in the detection of calcium. Intriguingly, however, LRNC percent was quite similar by VH-IVUS (10.8 ± 5.9) compared to that seen in the histopathological study ($11.6\% \pm 8.4\%$) (Table 1). Furthermore, the present study did not find a significant difference in the number of TCFA between diabetics and non-diabetics (7% vs 10% ; $P = .4$); this was also consistent with the finding of the histopathological study. It is quite reassuring that the biological insights gained from both VH-IVUS and CTA are consistent with data from histopathological observations and this positions both of these imaging modalities favorably in the assessment of atherosclerotic plaques.

IVUS-VH AND CORONARY CTA FOR ATHEROSCLEROTIC PLAQUE IMAGING

It is well-described and accepted that gray-scale IVUS is quite accurate in quantifying geometrical parameters of coronary atherosclerotic plaques. However, the role of tissue characterization with VH-IVUS, based on the information gained from the radiofrequency backscatter analysis of the reflected ultrasound profile, has been the topic of some controversy. While ex vivo validation studies have shown a strong correlation between histology and VH-IVUS findings, some in vivo studies have questioned the accuracy of this technology. Nevertheless, VH-IVUS still remains the best technology for the combined assessment of anatomy and tissue composition. Newer techniques, such as optical coherence tomography and near-infrared spectroscopy, may provide further advancements.

Figure 2. Three-dimensional reconstruction of VH-IVUS datasets. **A**, Calcium is shown as the blue to red color. **B**, Regions with VH-TCFA are shown in red on. *VH-IVUS*, Virtual histology intravascular ultrasound; *TCFA*, thin-cap fibroatheroma (Qian, Vazquez, Voros, 2009).

Although VH-IVUS is considered the “gold standard” for the evaluation of coronary atherosclerotic plaques, it is important to point out that there are some limitations. VH-IVUS is fundamentally a two-dimensional tomographic technique and three-dimensional information is gained by putting together the consecutive two-dimensional frames (Figure 2). Therefore, any length, and subsequently, any volume information depend on an accurate and consistent pullback of the ultrasound probe. While some studies have raised concerns about the accuracy of length measurements due to inconsistent pullback,¹⁵ the authors demonstrated excellent correlation to known distances in the coronary bed, increasing our confidence in the volumetric measurements.

It is also important to comment on the CT angiographic technique. The authors used conventional, 64-slice multi-slice computed tomography with a typical clinical protocol. It should be emphasized that CTA analysis was based on a qualitative, rather than a quantitative, approach. While this is consistent with current clinical practice, it limits the potential insights gained by this technique. Our group has recently shown that a highly standardized, quantitative approach is in fact quite reproducible and reliable. Furthermore, we have shown that using this quantitative approach we could demonstrate early vessel wall thickening without luminal compromise in asymptomatic patients without prior CAD but with intermediate/high Framingham Risk Score.¹⁰

Nevertheless, it is quite reassuring that the overall conclusions were similar to those gained by VH-IVUS. Although this study was not designed to compare the accuracy of coronary CTA to IVUS and VH-IVUS, the overall conclusions are consistent. Of note, there was no three-dimensional registration of the CT datasets with the VH-IVUS dataset. Preliminary work in our laboratory has shown that true three-dimensional registration is feasible and can be used to develop training algorithms for coronary CTA, using VH-IVUS as the “ground truth” (Figure 3).

Coronary CTA revealed a higher number of calcified plaques in diabetics (52% vs 24% ; $P < .001$), while Agatston score was not statistically significantly different ($282 [54-578]$ vs $85 [3-326]$; $P = .09$). This suggests that while the overall amount of calcium may not be different, diabetics have a larger number of smaller calcified plaques, perhaps as a result of more frequent intraplaque hemorrhage, healing and calcification.

While coronary CTA analysis in this study was qualitative, there are some preliminary data from our laboratory with a quantitative analysis in diabetics (preliminary, unpublished data) (Table 1). We found that plaque burden was approximately 57% in diabetic

Figure 3. True three-dimensional registration of non-contrast enhanced coronary calcium scans, contrast-enhanced coronary CTA, gray-scale IVUS and VH-IVUS. The three-dimensional registration interface is shown on the left panel. The right panel shows the corresponding cross-sectional view from the non-contrast-enhanced calcium scan, the contrast-enhanced coronary CTA, gray-scale IVUS and VH-IVUS (Qian, Voros, 2009).

plaques which were non-obstructive by fractional flow reserve measurements; this is larger than plaque burden found in most IVUS studies. This is most likely due to overestimation of plaque burden as a result of calcification and blooming artifact on coronary CTA. This is further supported by the finding that 36% of plaque burden was due to calcification, which is again higher than typical percentages seen in histopathology or IVUS. Importantly, low-density non-calcified plaque (–100–30 Hounsfield Units), which corresponded to the lipid-rich necrotic on some preliminary VH-IVUS studies, was approximately 10%, which is very similar to findings on histopathology.

In summary, the authors should be congratulated on a well-designed and well-done study. Both VH-IVUS and coronary CTA are clinical reality today and can be used in the appropriate setting to gain insight with regards to diabetic and non-diabetic atherosclerotic plaque geometry and composition. Since coronary CTA is non-invasive and can be performed with relatively low radiation exposure with some of the newer approaches (3–7 mSv range),¹⁶ it may be evaluated in carefully designed clinical trials for further risk stratification of symptomatic and asymptomatic high-risk individuals. Furthermore, coronary CTA may be applied to clinical trials of atherosclerosis modification. One such study is now underway in our laboratory, using combination therapy for atherosclerosis modification. IVUS and VH-IVUS remain the clinical “gold standard” for invasive characterization of atherosclerotic plaques today; the role of newer catheter-based techniques is now being evaluated in this setting. Such tools will further enable us to continue the fight against

atherosclerosis associated with the metabolic syndrome, diabetes and other metabolic abnormalities.

References

1. American Diabetes Association. Standards of medical care in diabetes—2009. *Diabetes Care* 2009;32:S13–61.
2. Razani B, Chakravarthy MV, Semenkovich CF. Insulin resistance and atherosclerosis. *Endocrinol Metab Clin North Am* 2008;37:603–21, viii.
3. Mazzone T, Chait A, Plutzky J. Cardiovascular disease risk in type 2 diabetes mellitus: Insights from mechanistic studies. *Lancet* 2008;371:1800–9.
4. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med* 1987;316:1371–5.
5. Burke AP, Kolodgie FD, Zieske A, et al. Morphologic findings of coronary atherosclerotic plaques in diabetics: A postmortem study. *Arterioscler Thromb Vasc Biol* 2004;24:1266–71.
6. Djaberi R, Beishuizen ED, Pereira AM, et al. Non-invasive cardiac imaging techniques and vascular tools for the assessment of cardiovascular disease in type 2 diabetes mellitus. *Diabetologia* 2008;51:1581–93.
7. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;15:827–32.
8. Akram K, O'Donnell RE, King S, Superko HR, Agatston A, Voros S. Influence of symptomatic status on the prevalence of obstructive coronary artery disease in patients with zero calcium score. *Atherosclerosis* 2008. doi:10.1016/j.atherosclerosis.2008.07.008.
9. Hoff JA, Quinn L, Sevrakov A, et al. The prevalence of coronary artery calcium among diabetic individuals without known coronary artery disease. *J Am Coll Cardiol* 2003;41:1008–12.
10. Akram K, Rinehart S, Voros S. Coronary arterial atherosclerotic plaque imaging by contrast-enhanced computed tomography: Fantasy or reality? *J Nucl Cardiol* 2008;15:818–29.
11. Min JK, Shaw LJ, Devereux RB, et al. Prognostic value of multidetector coronary computed tomographic angiography for

- prediction of all-cause mortality. *J Am Coll Cardiol* 2007;50:1161-70.
12. Nissen SE, Yock P. Intravascular ultrasound: Novel pathophysiological insights and current clinical applications. *Circulation* 2001;103:604-16.
 13. Nair A, Kuban BD, Tuzcu EM, Schoenhagen P, Nissen SE, Vince DG. Coronary plaque classification with intravascular ultrasound radiofrequency data analysis. *Circulation* 2002;106:2200-6.
 14. Serruys PW, Garcia-Garcia HM, Buszman P, et al. Effects of the direct lipoprotein-associated phospholipase A(2) inhibitor darapladib on human coronary atherosclerotic plaque. *Circulation* 2008;118:1172-82.
 15. Tanaka K, Carlier SG, Mintz GS, et al. The accuracy of length measurements using different intravascular ultrasound motorized transducer pullback systems. *Int J Cardiovasc Imaging* 2007; 23:733-8.
 16. Voros S. What are the potential advantages and disadvantages of volumetric CT scanning? *J Cardiovasc Comput Tomogr* 2009. doi: [10.1016/j.jcct.2008.12.010](https://doi.org/10.1016/j.jcct.2008.12.010).