

## Virtual histology assessment of atheroma at coronary bifurcations: colours at the crossroads?

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*The authors have no conflict of interest to declare.*

The treatment of lesions at bifurcations remains a technical challenge<sup>1-4</sup>. Interventions at these sites are associated, not only with a higher risk of acute complications, but also with higher restenosis rates<sup>1-6</sup>. During these procedures, either acute temporal deterioration of coronary flow or definitive lost of one of the distal coronary branches may occur<sup>1-6</sup>. In addition, in spite of initial success, suboptimal results are frequently obtained in these lesions, especially when assessed by accurate tomographic imaging techniques such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT)<sup>4-6</sup>. These suboptimal results may help to explain the higher risk for stent thrombosis and late restenosis<sup>4-6</sup>.

On the other hand, too many interventional strategies – some of them admittedly complex and time consuming – have been proposed to address these adverse anatomic scenarios<sup>4-7</sup>. This profusion of unsettled techniques simply reflects our failure to provide a clear answer to unmet needs. Indeed, full metal coverage of the origin of the three segments stemming from the bifurcation is sometimes required to ensure satisfactory geometric results. However, this aggressive approach often leads to important additional problems, namely coronary segments with a double metal layer or with significant stent malapposition<sup>4-6</sup>. Eventually, despite the vast array of sophisticated techniques (including dedicated stents) that theoretically guarantee optimal lumen reconstruction, results are not truly convincing: first, because of increased procedural complexity (there is always a price to pay in acute complication rates) and, second, due to disappointing long-term clinical and angiographic outcomes<sup>4-6</sup>.

Accordingly, the pendulum is swinging back to simple solutions that, whenever feasible, are currently being widely advocated, taking into consideration the efficacy demonstrated by the use of drug-eluting stents in this setting<sup>2,4</sup>. Furthermore, the pragmatism of accepting suboptimal angiographic result at the ostium of a jailed side branch (linear filling defect, haziness, focal narrowing) is gaining popularity considering that most alternative therapeutic options are not very attractive and might even jeopardise main branch results<sup>4</sup>. Moreover, unravelling the underlying aetiology of these ostial lesions may be quite difficult, and IVUS or OCT may be eventually required to disclose the presence significant atheroma burden versus stent jail or a carina shift effects<sup>6,8</sup>. Likewise, the use of the pressure wire has been advocated in this scenario to guide clinical decision making, since many angiographically severe lesions at the ostium of jailed side branches prove to have normal fractional flow reserve and, therefore, require no treatment<sup>9</sup>. Notably, even in cases with excellent angiographic results, these diagnostic techniques may unmask silent problems including: 1) significant stent protrusion from the side branch into the main vessel, 2) unintended stent gaps or inadequate scaffolding of the side branch ostium, 3) severe stent underexpansion and 4) stent malapposition<sup>2-8</sup>. To fully understand why bifurcation lesions are so challenging to treat it is therefore obvious that we need to gain further spatial insights into their complex three-dimensional architecture. However, is there anything else still missing? Clearly, the underlying pathologic substrate, namely tissue distribution and composition, appears to be another major player in this scenario, yet it has been poorly studied. Accordingly, new information on this aspect will be of critical value as well.

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## What is in a bifurcation? From anatomy to physiology and back to pathology

Classically, angiography has been the workhorse diagnostic tool to assess coronary bifurcations. Despite its well known limitations in this setting (foreshortening, vessel overlap, hidden ostia) many angiographic classification schemes eventually flourished. However, many of them were arbitrary, complex and without clear therapeutic implications and, as a result, soon became abandoned<sup>4</sup>. Currently, however, the Medina classification has been widely embraced to assess these lesions<sup>1,2</sup>. This classification scheme is highly appealing for its simplicity and practical value. However, further studies should correlate these readily identifiable angiographic patterns with the true spatial distribution of atheroma burden. Likewise, prognostic validation of this classification system will eventually facilitate tailoring available therapeutic strategies for specific anatomic challenges<sup>1,2</sup>.

However, only tomographic techniques can provide a comprehensive appraisal of the complex anatomic geometry encountered at coronary bifurcations. In a now classic study, Kimura et al<sup>9</sup> analysed the shape and position of atheroma at the most proximal segment of the left anterior descending coronary artery. Eccentric involvement was universal throughout the spectrum of stenosis severity. In addition, maximal plaque accumulation was located in the wall opposite to the flow divider (opposite to the circumflex take-off), but the carina was systematically spared. Most subsequent IVUS studies confirmed that the carina remains largely free from significant atherosclerotic changes<sup>10</sup>. This simple idea challenged the classical concept of “plaque shift” coined –historically– in the balloon era. Current knowledge suggests that, in most cases, the “snow-plow” phenomenon (leading to obstruction of the side branch origin), results from a carina shift phenomena rather than from true displacement of plaque material; although the latter can still be detected, especially in unstable patients with thrombus-laden lesions<sup>2,8</sup>. More recently, remodelling phenomena at bifurcations were studied. Shimada et al<sup>11</sup> suggested that outward remodelling with a concentric pattern is frequently observed in lesions proximal to the side branch, whereas inward remodelling with eccentric plaque distribution occurred in distal lesions. However, two separate IVUS pull-backs (main vessel and side branch) are actually required for a precise and thorough assessment of the geometry of bifurcation lesions<sup>12</sup>, although this remains cumbersome during routine clinical practice.

From a physiologic standpoint, bifurcations generate unique shear stresses at different vessel locations that have been extensively studied *in vitro* and *in vivo* in relation to the development of coronary atheroma<sup>13,14</sup>. Wall shear stress, the tangential, frictional force induced by flowing blood on the endothelial surface, appears to represent the most important local factor affecting atherogenesis and disease progression. Indeed, atherosclerosis tends to develop in areas of low shear stress as the result of endothelial dysfunction, increased uptake of lipoproteins, inflammation and smooth muscle cell proliferation<sup>14</sup>. Proximal vessels, inner segments of bends and bifurcations generate areas of oscillatory flow and low shear stress. Notably, a low shear stress is systematically detected at the “hips” of the bifurcation (walls opposite to the flow divider)<sup>14</sup>. The angle of

the bifurcation and the calibre of the side branch affect the amount of turbulence.

Major haemodynamic disturbances occur at coronary branch points. The good news is that these are governed by robust physiologic laws. Murray’s law states that, in optimal conditions (to follow the principle of minimum work), the cube of the radius of the main proximal vessel should equal the sum of the cubes of the radii of the daughter vessels<sup>15</sup>. Currently, virtual analysis of coronary bifurcations using computational fluid dynamics and finite-element modelling enable accurate flow predictions<sup>14</sup>. However, an exhaustive and precise anatomical and physiological assessment (including analysis of intravascular flow velocity profiles) is required to obtain comprehensive insights of wall shear stress characteristics and their relation with atherogenesis or neointimal growth after interventions<sup>14</sup>. Although shear stress has been classically related to plaque generation and its dominant distribution along the vessel circumference, surprisingly, scarce information exists regarding its influence on the genesis of distinct plaque components.

Last, but not least, seminal pathologic studies of bifurcation lesions revealed higher prevalence of atherosclerotic plaques at the walls opposite to the flow divider<sup>16</sup>. An interesting recent necropsy study by Nakazawa et al<sup>17</sup> in 26 coronary bifurcation lesions revealed that the lateral wall presented significantly greater intima and necrotic core thickness than the flow divider. Plaque thickness was the greatest on the lateral wall of the main daughter vessel followed by the lateral wall of the proximal main vessel. Interestingly, intima and necrotic core thickness was greater in the lateral wall of the main daughter vessel than in the lateral wall of the side branch. Notably, necrotic core was virtually absent in the carina. These investigators also demonstrated that in bifurcations treated with drug-eluting stents neointimal formation was less, whereas uncovered struts and fibrin deposition was greater at the flow divider compared with the lateral wall<sup>17</sup>. Notwithstanding the enormous interest of human pathology studies from patients with bifurcation lesions and cardiac death, findings at bifurcations lesions in living patients may significantly differ and, accordingly, clinical studies remain of major interest.

## Present studies

With virtual histology (VH), sophisticated autoregressive spectral analyses of raw radiofrequency signals are translated into a rainbow of persuasive colours encoding different plaque components<sup>18</sup>. This technology has been validated *ex vivo* and *in vivo* with good predictive accuracies for tissue characterisation. Previous studies suggested that necrotic core is more frequently found in unstable patients, proximal vessels and in lesions with positive remodelling, high strain or ruptures<sup>18</sup>. However, the value of VH in the three-dimensional characterisation of the underlying substrate of bifurcation lesions has not been previously established.

In this issue of EuroIntervention, García-García et al<sup>19</sup> from the Thoraxcenter (Rotterdam, The Netherlands) and Han et al<sup>20</sup> from the Mayo Clinic (Rochester, MN, USA), present two closely related studies where VH was specifically used to assess tissue composition at coronary bifurcations. These studies are methodologically sound and complementary in nature, providing unique and novel information that expands our previous knowledge in this exciting field.

García-García et al<sup>19</sup> compared the distribution of several plaque components between bifurcation (n=108) and non-bifurcation (n=112) lesions in a total of 129 patients included in the Volcano Registry. Necrotic core characteristics were thoroughly analysed. Overall, the relative compositional analysis revealed no major differences in tissue characteristics along different axial locations in bifurcation and in non-bifurcation lesions. However, in bifurcation lesions, a necrotic core “in contact with the lumen” was more frequently found in the downstream plaque segment. Conversely, although not statistically significant, the amount of necrotic core in non-bifurcation lesions tended to be larger in the upstream segment. Notably, total plaque burden and necrotic core area were significantly larger in bifurcation than in non-bifurcation lesions. Finally, thin-cap fibroatheromas were also more frequently detected at bifurcation lesions but, again, these were evenly distributed between upstream and downstream bifurcation segments<sup>19</sup>. The authors concluded that the larger plaque burden and necrotic core component in bifurcation lesions may explain the relative adverse outcomes seen in the treatment these lesions. This hypothesis is highly plausible, because previous IVUS and VH studies have demonstrated the correlation of these adverse features with distal embolisation and myonecrosis<sup>18</sup>.

Han et al<sup>20</sup> analysed with VH the tissue characteristics of atherosclerotic plaques in 256 coronary bifurcations from 237 patients. Interestingly, in left-main bifurcation lesions, the distal segments had larger plaque burden, percentage of necrotic core and percentage of dense calcium, as compared with more proximal segments. However, exactly the opposite was true in non-left main bifurcations (those located in the left anterior descending, right or circumflex coronary arteries) where plaque burden, percentage of necrotic core and percentage of dense calcium, were significantly greater in the proximal segment of the bifurcation. These investigators suggested that there is heterogeneous, non-uniform, distribution of histopathologic tissue content between bifurcation lesions at the left main and other bifurcation locations<sup>20</sup>. This study did not include a control group to assess whether this distinct component distribution – according to vessel territory – also affected lesions not located at bifurcations. It is well known that the left main is rich in elastic fibres which extend to some extent into the most proximal part of the left anterior descending coronary artery. Therefore, strain factors may play a predominant role at this unique location; whereas in other vessels, geometrically-related shear stress may be more closely implicated in plaque distribution and composition.

Virtually an identical methodology was followed by the two groups to obtain volumetric VH data as well as to perform the compositional analyses and, in fact, the same core lab was used in both studies<sup>19,20</sup>. However, the two studies significantly differed with respect to the definition of proximal and distal segments. In the study from Rotterdam<sup>19</sup>, proximal and distal segments were of variable length and defined according to the location of the lesion minimal lumen area (that actually was distal to the side branch take-off in 52% of cases). Therefore, lesion components were analysed with respect to the location of lesion minimal lumen area (upstream and downstream), but not exactly in relation to the side

branch origin. Alternatively, in the Rochester study<sup>20</sup>, proximal and distal coronary segments were, by definition, 5 mm in length each, and were precisely separated by the side branch take-off. Other differences between the studies were that the left main bifurcations were not analysed in the Thoraxcenter study<sup>19</sup>, whereas a control group of non-bifurcation lesions was not available in the Mayo Clinic study<sup>20</sup>.

Some interesting issues should be highlighted:

First, most lesions in these studies were non-obstructive with mild atherosclerosis on IVUS<sup>19,20</sup>, but additional angiographic insights on lesion severity (minimal lumen diameter and percent diameter stenosis) would have been of interest. However, with a mean minimal lumen area of 5 mm<sup>2</sup> and plaque burden of 64%, it is likely that some of these lesions were close to a borderline physiologic significance<sup>19</sup>. In the study of Han et al<sup>20</sup>, 15% of the lesions had significant disease (plaque burden >75%). Neither study, however, presented a correlation between tissue characteristics and lesion severity, yet this would have been helpful to ascertain the value of potential extrapolations to findings in severe bifurcation lesions.

Second, the detailed compositional analyses of both studies were not matched with the geometric structure of the vessel and, in particular, tissue characteristics were not examined in relation to areas of different shear stress<sup>19,20</sup>. Although upstream segments were nicely compared with those downstream, no analysis was performed to disclose the location of the bulk of the plaque with respect to the carina or, even of greater interest, the potential preferential circumferential distribution of specific plaque components with respect to the flow divider. The absence of plaque at the carina may hamper such analysis, but data on plaque characteristics at other sites would have been of major interest. In a previous non-volumetric study using VH and OCT, Gonzalo et al<sup>21</sup> suggested that the percentage of necrotic core was higher, and the fibrous cap thinner, at the proximal “rim” of the bifurcation. This information appears to be largely concordant with the data of Han et al<sup>20</sup> in non-left main bifurcations. Furthermore, although in the current Rotterdam study<sup>19</sup> the percentage of necrotic core had a uniform axial distribution along the plaque, the absolute amount of necrotic core was significantly greater at its proximal segment.

Third, precise data on lesion location in the coronary tree (proximal, mid and distal coronary segments) were not presented in these studies, yet this would have been of value. Clinical, angiographic and IVUS studies suggest that most vulnerable plaques tend to be proximally located and, therefore, findings of both studies might have been affected by an uneven distribution of proximal lesions.

Fourth, in the two studies, imaging was only performed from the main branch. Therefore the ostium of the side branch was not adequately studied, and yet this has been considered the Achilles’ heel of interventions in bifurcation lesions<sup>1-6</sup>. Likewise, curves in the main vessel, the angle of the side branch take-off and the diameters of daughter vessels were not analysed to be related with the study findings. Besides, in the study of García-Gracia et al<sup>19</sup>, lesion length and lesion severity was different between bifurcation and non-bifurcation lesions and, again, this might had had some influence in their results.

Finally, general limitations of current VH technology should be kept in mind to obtain a correct perspective<sup>18</sup>. Thrombus is not recognised by the encoding algorithm, and tends to be depicted as fibrous tissue. Poor radiofrequency signals from areas behind calcium may provide misleading characterisation of tissue, eventually codified as necrotic core. Lumen and external elastic lamina areas may be difficult to delineate at the site of side branch exit (interpolations are required), and this may affect reliability of geometric and compositional analyses. Finally, non-uniform pull-back speed may limit volumetric analyses<sup>18</sup>. However, most of these factors are unlikely to significantly affect the results of the present studies.

## Final remarks

Addressing unmet geometrical needs during interventions in bifurcation lesions remains a challenge. Further, identification of the pathophysiology of “vulnerable bifurcations” also remains elusive. However, studies to further elucidate the implications of the unique underlying substrate of coronary bifurcations should not be longer considered just as an elegant academic exercise. In aggregate, the information provided by the two studies presented in this issue of *EuroIntervention* highlight the importance of assessing plaque composition and opens new research venues.

Should the distinct compositional patterns detected by these studies be confirmed in severe bifurcation lesions, they may have profound implications. The adverse compositional characteristics (greater plaque burden and necrotic core) of these lesions are likely implicated in the higher rate of procedural-related complications. Therefore, the potential value of aggressive pharmacologic prevention therapy should be investigated. Likewise, the distinct substrate of left main versus non-left main bifurcations may also bear therapeutic consequences. Special care should be paid to completely cover with stents the proximal aspect of non-left main bifurcations and the distal segment in left main bifurcations. Although compositional analyses have not yet been clearly associated with long-term clinical events, it appears reasonable to speculate that both restenosis rate and risk for stent thrombosis may be influenced by adverse compositional characteristics. Hopefully, a better characterisation of bifurcation lesions will soon lead to improved interventional strategies and tailored therapies and, eventually, to better long-term clinical outcomes.

## References

1. Medina A, Suárez de Lezo J, Pan M. A new classification of coronary bifurcation lesions. *Rev Esp Cardiol*. 2006;59:183.
2. Medina A, Suárez de Lezo J. Percutaneous coronary intervention in bifurcation lesions. Does classification aid treatment selection? *Rev Esp Cardiol*. 2009;62:595-8.
3. Alfonso F, Hernández C, Pérez-Vizcayno MJ, Hernández R, Fernández-Ortiz A, Escaned J, Bañuelos C, Sabaté M, Sanmartín M, Fernández C, Macaya C. Fate of stent-related side branches after coronary intervention in patients with in-stent restenosis. *J Am Coll Cardiol*. 2000;36:1549-56.
4. Hildick-Smith D, Lassen JF, Albiero R, Lefevre T, Darremont O, Pan M, Ferenc M, Stankovic G, Louvard Y. Consensus from the 5th European Bifurcation Club meeting. *EuroIntervention*. 2010;6:34-8.
5. Routledge HC, Lefèvre T, Colombo A, Oldroyd KG, Hamm CW, Guagliumi G, von Scheidt W, Guetta V, Ruzyllo W, Wittebols K, Goedhart DM, Serruys PW. Three-year clinical outcome of percutaneous treatment of bifurcation lesions in multivessel coronary artery disease with the sirolimus-eluting stent: insights from the Arterial Revascularisation Therapies Study, part II (ARTS II). *EuroIntervention*. 2009;5:190-6.
6. Lefèvre T, Ormiston J, Guagliumi G, Schultheiss HP, Quilliet L, Reimers B, Brunel P, Wijns W, Buettner HJ, Hartmann F, Veldhof S, Miquel K, Su X, van der Giessen WJ. The Frontier stent registry: safety and feasibility of a novel dedicated stent for the treatment of bifurcation coronary artery lesions. *J Am Coll Cardiol*. 2005;46:592-8.
7. Heras M, Avanzas P, Bayes-Genis A, Pan M, Pérez de Isla L, Sanchis J. Unplanned redundant publication: a consequence of too many cardiovascular journals? *EuroIntervention*. 2010;6:179-81.
8. Koo BK, Waseda K, Kang HJ, Kim HS, Nam CW, Hur SH, Kim JS, Choi D, Jang Y, Hahn JY, Gwon HC, Yoon MH, Tahk SJ, Chung WY, Cho YS, Choi DJ, Hasegawa T, Kataoka T, Oh SJ, Honda Y, Fitzgerald PJ, Fearon WF. Anatomic and functional evaluation of bifurcation lesions undergoing percutaneous coronary intervention. *Circ Cardiovasc Interv*. 2010;3:113-9.
9. Kimura BJ, Russo RJ, Bhargava V, McDaniel MB, Peterson KL, DeMaria AN. Atheroma morphology and distribution in proximal left anterior descending coronary artery: in vivo observations. *J Am Coll Cardiol*. 1996;27:825-31.
10. Badak O, Schoenhagen P, Tsunoda T, Magyar WA, Coughlin J, Kapadia S, Nissen SE, Tuzcu EM. Characteristics of atherosclerotic plaque distribution in coronary artery bifurcations: an intravascular ultrasound analysis. *Coron Artery Dis*. 2003;14:309-16.
11. Shimada Y, Courtney BK, Nakamura M, Hongo Y, Sonoda S, Hassan AH, Yock PG, Honda Y, Fitzgerald PJ. Intravascular ultrasonic analysis of atherosclerotic vessel remodeling and plaque distribution of stenotic left anterior descending coronary arterial bifurcation lesions upstream and downstream of the side branch. *Am J Cardiol*. 2006;98:193-6.
12. van der Waal EC, Mintz GS, Garcia-Garcia HM, Bui AB, Pehlivanova M, Girasis C, Serruys PW, van der Giessen WJ, Weissman NJ. Intravascular ultrasound and 3D angle measurements of coronary bifurcations. *Catheter Cardiovasc Interv*. 2009;73:910-6.
13. van der Giessen AG, Wentzel JJ, Meijboom WB, Mollet NR, van der Steen AF, van de Vosse FN, de Feyter PJ, Gijzen FJ. Plaque and shear stress distribution in human coronary bifurcations: a multislice computed tomography study. *EuroIntervention*. 2009;4:654-61.
14. Alfonso F. Haemodynamic findings after drug-eluting stenting: expected, provocative, or challenging? *Eur Heart J*. 2006;27:1764-6.
15. Murray CD. The physiological principle of minimum work. I, The vascular system and the cost of blood volume. *Proc Natl Acad Sci USA*. 1926;12:207-14.
16. Fox B, James K, Morgan B, Seed A. Distribution of fatty and fibrous plaques in young human coronary arteries. *Atherosclerosis* 1982;41:337-47.
17. Nakazawa G, Yazdani SK, Finn AV, Vorpahl M, Kolodgie FD, Virmani R. Pathological findings at bifurcation lesions. The impact of flow distribution on atherosclerosis and arterial healing after stent implantation. *J Am Coll Cardiol* 2010;55:1679-87.
18. Alfonso F, Hernando L. Intravascular ultrasound tissue characterization. I like the rainbow but... what's behind the colours? *Eur Heart J*. 2008;29:1701-3.



19. García-García HM, Gomez-Lara J, Gonzalo N, Garg S, Shin ES, Goedhart D, Serruys PW. A comparison of the distribution of necrotic core in bifurcation and non-bifurcation coronary lesions: An in vivo assessment using intravascular ultrasound radiofrequency data analysis. *EuroIntervention* 2010;6:321-327.

20. Han SH, Puma J, García-García H, Nasu K, Margolis P, Leon MB, Lerman A. Tissue characterization of atherosclerotic plaque in coronary

artery bifurcations: an intravascular ultrasound radiofrequency data analysis in humans. *EuroIntervention* 2010;6:313-320.

21. Gonzalo N, Garcia-Garcia HM, Regar E, Barlis P, Wentzel J, Onuma Y, Ligthart J, Serruys PW. In vivo assessment of high-risk coronary plaques at bifurcations with combined intravascular ultrasound and optical coherence tomography. *JACC Cardiovasc Imaging*. 2009;2:473-82.