European Heart Journal (2011) **32**, 261–263
doi:10.1093/eurheartj/ehq314

EDITORIAL

Aiming at a disorder's concept by 3D QCA vs. FFR: a case of advanced ballistics

Christian Seiler*

Department of Cardiology, University Hospital, CH-3010 Bern, Switzerland

Online publish-ahead-of-print 9 September 2010

This editorial refers to 'Three-dimensional and two-dimensional quantitative coronary angiography, and their prediction of reduced fractional flow reserve'†, by A.S.C. Yong *et al.* on page 345

'Oculo-stenotic reflex' is a term which ridicules the variably developed attraction of interventional cardiologists to 'seal' coronary atherosclerotic bumps by balloon angioplasty. Its serious template relates to their daily business of estimating the functional relevance of a coronary stenosis by its structure. It is well known that even the experienced interventionalist may be 'lost in translation' when it comes to judging intermediate severity stenoses.[1] Long before the development of intracoronary sensor guidewires for functional stenosis assessment, attempts were made to improve the structure–function translation by quantitative coronary angiography (QCA) as obtained in two (2D), but also as reconstructed in three dimensions (3D).[2,3] The two principles of any coronary structure–function translation are (i) statistical comparison of single, physically important structural stenosis elements with a functional reference; and (ii) the mathematical integration of stenosis' geometric hallmarks to a single measure with subsequent statistical reference comparison.

Ideally, both approaches would have to anticipate all the geometric patterns of a coronary atherosclerotic lesion, because it is the composite of all its finite structural elements which determines the drop in flow or perfusion pressure. Thus, the method would be aiming at a disorder's concept (i.e. recognition of how exactly and variably the epicardial stenoses grow in coronary artery disease; CAD). In philosophical terms, 'a disorder's concept' is an oxymoron and, therefore, pointing at it probably unsuccessful. In geometrical terms and as outlined below, it is challenging to model the structural elements of a stenosis accurately into a haemodynamic parameter.

Notwithstanding these considerations, Yong and co-workers have observed, on a purely statistical basis, 2D- and 3D-QCA parameters and compared them with coronary pressure-derived fractional flow reserve (FFR) as the functional reference (FFR $= P_d/P_{ao}$, where P_d is the mean distal coronary pressure and P_{ao} is the mean aortic pressure).[4] The prime conclusion of the thorough work, for which the authors have to be commended is not unexpected: 'the accuracy of QCA in predicting functionally significant FFR is limited . . . '.

The present study

In 63 CAD patients undergoing elective percutaneous coronary intervention (PCI) of 63 atherosclerotic lesions, Yong *et al.* compared the 2D- and 3D-QCA-derived percentage diameter stenosis, minimal vessel lumen diameter (MLD), lesion length, minimal luminal cross-sectional area (MLA), and the percentage area stenosis with FFR.[4] 3D-QCA reconstruction by a customized software was performed offline on the basis of two orthogonal angiographic views of the target lesion in the ECG-triggered, end-diastolic frame. 2D-QCA-derived MLD correlated best and directly with FFR at an r^2 linear regression coefficient of 0.34, and MLA obtained by 3D-QCA correlated best and directly with FFR at an r^2 linear regression coefficient of 0.40. Receiver operating characteristics analysis showed that an MLD $\leq$1.25 mm (best cut-off) as measured by 2D-QCA predicted a pathological FFR $<$0.75 with a sensitivity of 3/4 and a specificity of 2/3; an MLA $\leq$1.60 mm^2 (best cut-off) as measured by 3D-QCA predicted a pathological FFR $<$0.75 with a sensitivity and specificity of 4/5. Statistically, the moderate linear regression coefficients for the association between structural (x-axis on their figure 4) and functional (y-axis) parameters were improved to an r^2 value of $\sim$0.5 when applying a minus x^{-1} function (best fit mathematical model), whereby—counter-intuitively—2D-QCA MLD was related more closely to FFR than 3D-QCA MLA.

Which are the sources of all that 'noise' in the relationship between structural coronary parameters and their functional reference? Its level is considerable, i.e. 50–76% of the variability between structural and functional parameters relate to parameters others than MLD, MLA, and FFR. By statistical definition, FFR is the independent reference variable, assuming MLD and MLA as the

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

* Corresponding author. Tel: 41 31 632 36 93, Fax: +41 31 632 42 99, Email: christian.seiler@insel.ch

† doi:10.1093/eurheartj/ehq259

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2010. For permissions please email: journals.permissions@oup.com.

source: https://doi.org/10.7892/boris.1604 | downloaded: 12.10.2024

suspects and culprits of the poor relationship. From a biophysical standpoint, such a notion has to be challenged by interrogating FFR as well as QCA.

Critique of QCA

Though they are quantitatively obtained parameters, each of the numerous individual factors such as MLD, MLA, percentage diameter stenosis, etc., does just partially account for the perfusion pressure drop across a stenotic lesion (ΔP). Even in the geometrically simple setting of a focal coronary stenosis created artificially by a circumferential balloon constrictor, the pressure drop is a quadratic function of pressure loss due to viscous friction (f) and flow (Q) separation (s):[5] $\Delta P = fQ + sQ^2$. The viscous friction pressure loss coefficient f is determined by the stenosis length (L) and—inversely—by the minimal cross-sectional area (A_s; $f = L/A_s \times 1/A_s$). The flow separation pressure loss coefficient s is influenced by the difference between the luminal cross-sectional area of the stenotic and the non-stenotic (A_n) part of the vessel $[(1/A_s - 1/A_n)^2]$. Furthermore, the pressure drop is affected by the blood viscosity and its density, by the flow velocity profile, and by a geometric factor mostly not accounted for, i.e. the stenosis entrance and exit angle. The contribution of all these factors would favour the description of their haemodynamic result (pressure drop) by a quadratic or even a cubic equation. Thus, the above-mentioned result of the study of Yong and co-workers[4] that the best fit between MLD an MLA and FFR, respectively, is a minus x^{-1} function does not—physically—describe the entire model. Particularly, it is unreasonable that 2D- and 3D-QCA data fit similarly well to FFR by the same minus x^{-1} function.

In the above context, a 3D view of the target lesion might be preferable over a 2D aspect, because factors such as the minimal cross-sectional area, the lesion length, and the entrance and exit angle, which vary according to the eccentricity of a stenosis, could be better accounted for. *Figure 1* illustrates the value of two orthogonal views of a stenosis in the context of an eccentric lesion: the left main coronary artery dissection leading to a very severe eccentric lesion may be missed in one plane. However, it

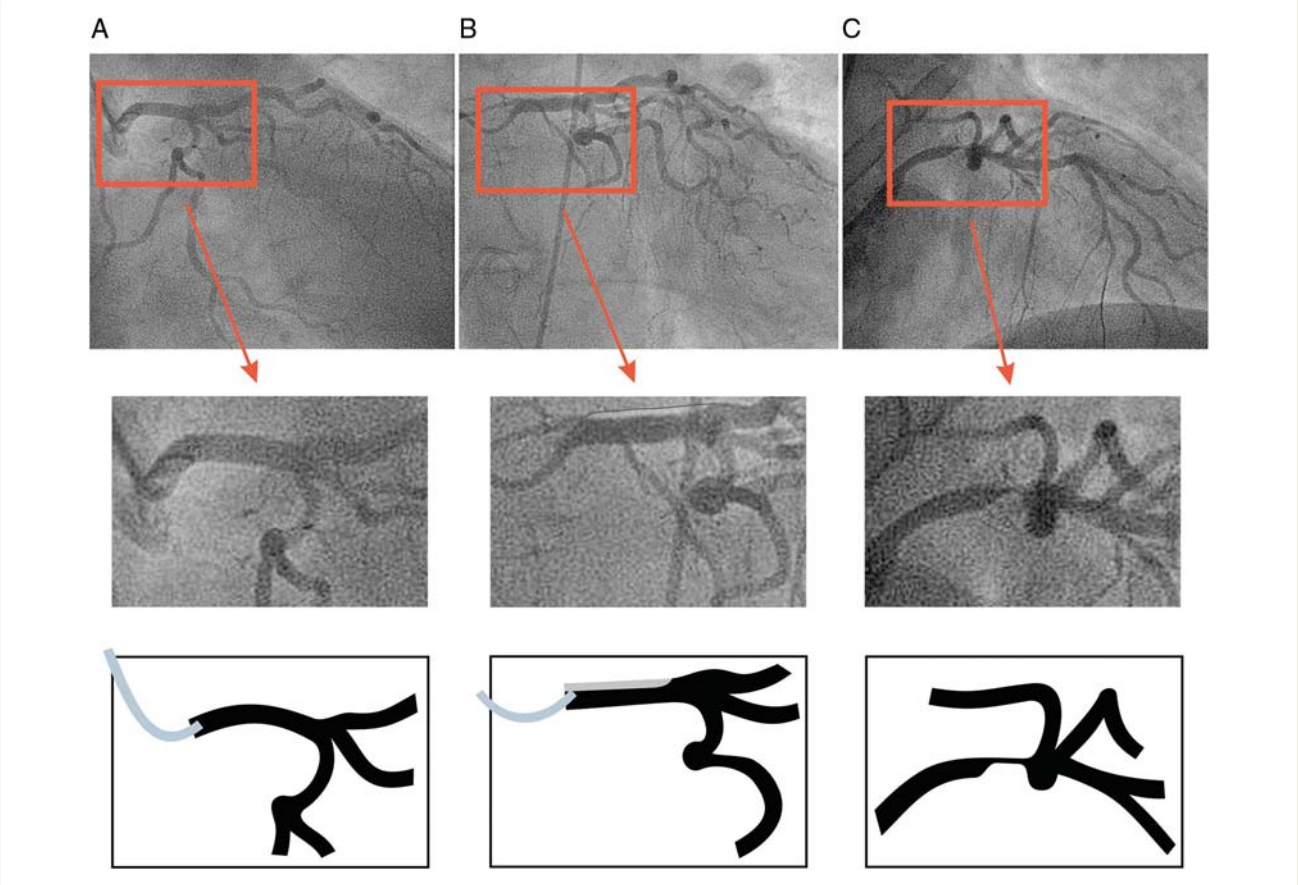

Figure 1 Coronary angiogram with magnified views (middle rows) and schematic drawings (bottom rows) of the left coronary artery obtained at different time points during the exam (columns *A*, *B*, and *C*). The angiogram in column *A* is taken at the start of the exam. The AP caudal view shows a normal left main coronary artery. The angiogram in column *B* (AP view) is taken 5 min later following the attempt at coronary intubation by an Amplatzer AL2 catheter. The patient went into cardiogenic shock. The discrete haziness at the cranial border of the left main coronary artery is hardly visible; it is schematically illustrated in the drawing at the bottom of column *B*. The angiogram in column *C* (AP cranial view) is taken only after implantation of a left ventricular assist device; a tight distal left main stenosis becomes visible.

has to be considered that the 3D coronary angiography employed in the present study is not 'real-space' or real-time 3D (with 15 images/s), but just a reconstructed 2D image on the basis of two image planes. The algorithm employed for the 3D reconstruction may be more decisive for the parameters obtained than the real stenosis geometry.

Critique of FFR

The haemodynamic reference used (FFR) is not as solid as suggested, but rather a moving target at which the 'gun' of QCA has been pointed. FFR may have substantially contributed to the moderate correlation found in the study of Yong *et al.* between structural and functional coronary parameters.[4] FFR is a coronary pressure-derived haemodynamic parameter, and the 'F' in 'fractional *F*low reserve' can only be described by a pressure if certain conditions are fulfilled. On the basis of Ohm's law ($\Delta P = RQ$, where R is vascular resistance), the most interesting, but difficult to obtain, flow-rate Q is mirrored by the coronary pressure drop ΔP or by FFR only if R is constant. Theoretically, the constancy of R in the coronary microcirculation can be reached by maximal vasodilation. The vasodilator employed for that purpose is adenosine intravenously (i.v.) at a rate of 140 μg/min/kg. One of the first sources of varying FFR values in the present study is that the dose and route of application changed between i.v. at the above rate and intracoronary at a dose which is four times higher than that used in the literature. Also, ΔP can only be substituted for Q if there is no change in R by the perfusion pressure in the microcirculation, i.e. if there is no coronary distensibility (higher resistance with diminished perfusion pressure). Both described assumptions related to a constant and minimal resistance[6] are probably erroneous,[7] because in comparison with the experimental model, it is hard to achieve maximal vasodilation using the mentioned i.v. dose of adenosine, and because the coronary circulation actually seems to be distensible.[8] Furthermore, a variable degree of collateral flow to the vascular area downstream of a stenosis influences the distal coronary pressure with identical variability, e.g. the FFR obtained during vascular occlusion can be as high as 0.8 despite the occlusion.[8] Finally, and for research puposes, FFR should be calculated by accounting for central venous pressure (CVP) as $(P_d - CVP)/(P_{ao} - CVP)$. In the presence of a tight stenosis without collateral flow, the assumption that CVP = 0 mmHg leads to an overestimation of FFR.

Clinical implications

For routine clinical and not for research purposes, the present study's conclusion can be kept in mind: 'the accuracy of QCA in predicting functionally significant FFR is limited . . . '. In addition, it is probably reversible: 'The accuracy of FFR in predicting a structurally significant stenosis by QCA is limited . . . '. Thus and despite the findings of the FAME study,[9] we may retreat to a lean practice of PCI by taking into account the patient's history, stress ECG, and an experienced estimate of the angiographic stenosis severity in several planes.

Conflict of interest: none declared.

References

1. White C, Wright C, Doty D, Hiratza L, Eastham C, Harrison D, Marcus M. Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis? *N Engl J Med* 1984;**310**:819–824.
2. Harrison D, White C, Hiratzka L, Doty D, Barnes D, Eastham C, Marcus M. The value of lesion cross-sectional area determined by quantitative coronary angiography in assessing the physiologic significance of proximal left anterior descending coronary arterial stenoses. *Circulation* 1984;**69**:1111–1119.
3. Seiler C, Kirkeeide RL, Gould KL. Basic structure–function relations of the epicardial coronary vascular tree. Basis of quantitative coronary arteriography for diffuse coronary artery disease. *Circulation* 1992;**85**:1987–2003.
4. Yong ASC, Ng ACC, Brieger D, Lowe HC, Ng MKC, Kritharides L. Three-dimensional and two-dimensional quantitative coronary angiography, and their prediction of reduced fractional flow reserve. *Eur Heart J* 2011;**32**:345–353. First published on 12 August 2010. doi:10.1093/eurheartj/ehq259.
5. Gould K. Pressure–flow characteristics of coronary stenoses in unsedated dogs at rest and during coronary vasodilation. *Circ Res* 1978;**43**:242–253.
6. Pijls NHJ, van Son JAM, Kirkeeide RL, de Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous coronary angioplasty. *Circulation* 1993;**86**:1354–1367.
7. Spaan J, Piek J, Hoffman J, Siebes M. Physiological basis of clinically used coronary hemodynamic indices. *Circulation* 2006;**113**:446–455.
8. Seiler C. *Collateral circulation of the heart*, Vol 1. London: Springer; 2009.
9. Tonino P, De Bruyne B, Pijls N, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd K, Ver Lee P, MacCarthy P, Fearon W, FAME Study InvestigatorsFractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;**360**:213–224.