# All that glisters is not gold: the elusive difference between statistics and pathophysiology

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"All that glisters is not gold."
William Shakespeare, Merchant of Venice, Act II Scene 7

It is an accepted concept that coronary artery disease (CAD) does not coincide with coronary artery obstruction.[1] Most recent data point out that a major proportion of patients presents with CAD symptoms without > 50% vessel stenosis, and ischemia in patients without coronary obstruction is a well-known reality, with significant prognostic implications.[1,2] An important consequence of this notion is that functional characterization of vessel status is needed to proper orient therapy. Several techniques have been developed to this aim, either to be applied during catheterization, such as fractional flow reserve (FFR), or to quantitatively analyze the angiographic images, such as quantitative flow reserve (QFR).[3,4] In this last instance, the contrast medium flow is transformed in pressure data, based on various assumptions.[4,5] A further and most recent development of this approach is the use of QFR to derive a virtual pull-back analysis, which, as the catheter equivalent, should allow identifying whether there is a diffuse coronary involvement or a focal obstruction.[6,7] In particular, the pull-back pressure gradient (PPG) is a continuous variable that considers the relationship of pressure gradient in the vessel segments with the overall coronary artery gradient and therefore can vary between 0, which indicates diffuse disease without stenosis, to 1, which implies a single significant obstruction.[6] The validation of the virtual QFR PPG using quantitative PET has been recently published and the Authors have stressed the potential relevance of the parameter for improving the detection of diffuse coronary artery disease.[7]

In the present issue of the Journal of Nuclear Cardiology, the same first Author with other coworkers proposes another validation of the QFR PPG.[8] They use as reference a different method for quantifying myocardial blood flow (MBF), i.e., dynamic CZT SPECT, a technique that offers the potential advantage of wider and easier accessibility as compared with the more expensive and demanding quantitative myocardial PET.[9,10] Moreover, since QFR PPG has been proposed for the recognition of diffuse CAD they have expanded the panel of quantitative CZT SPECT to include not just MBF, myocardial flow reserve (MFR) and relative flow reserve (RFR), but also the longitudinal flow gradient, as well as its delta between stress and rest. These last variables have been so far applied to PET studies with the main purpose of differentiating between MBF abnormalities caused by epicardial disease and coronary microvascular dysfunction. They can improve the recognition of diffuse CAD, for instance in preclinical atherosclerosis, as well as be a useful additional parameter for diagnosing CAD.[11–15]

So far, so good: it could be assumed that the present paper by Neng Dai et al. fills a gap in our knowledge about functional characterization of CAD.[8] At a first sight the results confirm the value of virtual QFR PPG, because it fairly correlates with longitudinal MBF gradient and is similarly effective for detecting the vessels with ischemia, defined as either an abnormal RFR or abnormal QFR. At a more attentive evaluation, however, there are several flaws that limit the value of these apparently straightforward conclusions. A first point is

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the patient selection: after having applied several exclusion criteria, the selected group of 50 patient is further reduced to slightly more than a half because of technical issues, most probably involving the angiographic methodology. The Authors minimize the 20% dropout rate for the vessels as the consequence of a still not fully optimized methodology, to be improved in the future. In terms of patients, however, this implies a 44% dropout rate, a circumstance that heavily affects the clinical reliability and applicability of the study results. Second, the reference standard for ischemia, either noninvasive, RFR, or angiographic, QFR, does not differentiate whether the cause is focal obstruction or diffuse vessel disease. Unfortunately, the Authors do not provide any clear statement about the angiographic status of the (very few) examined vessels. Indeed, the reported QFR PPG values in this patient cohort are nearer to 1 (and thus suggestive for the prevalence of segmental stenosis) than to 0 (which would mean diffuse disease) and are clearly higher than in the patient population of the previously published PET comparison.[6,7] Regarding the longitudinal gradient, two observations are necessary. The reported values appear noticeably larger than the corresponding PET figures: for instance, in the paper by Valenta et al. the stress gradient ranges between − 0.09 in normal controls and − 0.28 in CAD patients, whilst in the present article the values range from 2.22 in vessels with normal RFR to 1.14 in those with RFR $\leq$ 0.80.[8,13] Similarly, larger values are reported for the delta of the gradient between stress and rest.[8,13] The missing detailed description of the segmental MBF makes difficult to understand the reasons of these differences, but they could imply that CZT SPECT does not provide a equally reliable assessment of the longitudinal gradient, a circumstance that cannot be excluded because of the absence of prior validation studies and of the various potential limitations of the CZT SPECT technique, such as the lower resolution, partial volume effect, and the missing attenuation correction.[16] A second point is that the longitudinal gradient can be abnormal in case of both diffuse disease and segmental vessel obstructions, particularly if these are not proximal.[15,17] This again requires that the visual vessel status is otherwise known. Since the sole adopted references, RFR and QFR, are unable to differentiate between ischemia caused by segmental obstruction versus diffuse disease, according to the study design as it is described, its results cannot define the specific value of QFR PPG and longitudinal MBF gradient using CZT SPECT for detecting diffuse coronary vessel involvement.

In conclusion, although pursuing the commendable aspiration to expand our knowledge about methods capable of recognizing diffuse CAD, being based just on the simplistic logic of directly comparing the values of two of them, the study fails to provide really sound evidence for their usefulness, nor it is able to exclude it. In more general terms, this paper seems an example of the possible dangers of expanding comparative studies without considering the complex pathophysiology of coronary circulation in CAD, in which each parameter may catch just one of the several faces of vessel dysfunction.[11] Unfortunately, not every conceivable comparison is as well reasonable and useful. No significant correlation or statistical difference, and even if much more impressing than those reported in the present study, can overcome the lack of an attentive conceptual evaluation of the pathophysiological meaning of the matched variables.

## Disclosure

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

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