How accurate is the accuracy?

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In this issue of JNC, Cho et al[1] present a meta-analysis of 10 papers, published in 2009-2017, with the goal to compare the diagnostic accuracy of PET-derived myocardial blood flow (MBF) parameters, which would presumably advance non-invasive diagnostics of CAD. Compared diagnostic metrics included hyperemic MBF (hMBF), myocardial flow reserve ratio (MFR), and relative flow reserve—RFR, the ratio of hyperemic MBF in a stenotic area to hyperemic MBF in a normally perfused area, also known as FFR_{PET}.[2] Authors selected 10 studies out of 116, based on pre-specified inclusion criteria, which included either FFR or anatomical definition of hemodynamically significant coronary stenosis. Analysis was carried on a per vessel basis (2522 from 1099 patients).

Pooled sensitivity (95% CI) was highest for hMBF—0.85 (0.82-0.88), followed by MFR—0.76 (0.71-0.79) and RFR—0.64 (0.54-0.73). Pooled specificity (95% CI) was numerically greater for RFR [0.90 (0.86-0.93)] though overlapped with hMBF [0.84 (0.83-0.86)] and both were somewhat larger than MFR [0.80 (0.78-0.82)]. Pooled AUC ± SEM of hMBF (0.90 ± 0.02) was higher than of RFR (0.84 ± 0.05) and both were larger than of MFR (0.83 ± 0.03). The authors concluded that hyperemic MBF showed the best sensitivity, while RFR showed the best specificity in the diagnosis of significant coronary stenosis. MFR was less sensitive than hMBF and less specific than hMBF and RFR.

Authors state that 'systematic review and meta-analysis among different MBF parameters measured by PET have never been conducted' and theirs is the first one. Although technically it is not so—for instance, in September 2018 a meta-analysis[3] discussed diagnostic value of several non-invasive tests, PET included—the study of Sang-Geon Cho et al[1] brings up an important issue of pooling the myocardial perfusion PET data to get to a higher level of understanding it and, later, using it in clinics. Apart from only analyzing papers written in English, authors formulated four inclusion criteria: a per-vessel basis analysis performed in ≥ 10 arteries; clinical studies with absolute numbers of true positive, false negative, true negative, and false positive cases; stable CAD without structural heart disease; and fractional flow reserve (FFR) and/or anatomical stenosis severity measured as diameter stenosis (DS) by invasive coronary angiography as reference standards of significant coronary stenosis. The authors, however, take for granted the idea that the values of myocardial perfusion—hMBF, MFR, RFR—can be pooled. Yet, may they be?

As Gould et al state in 2013, 'studies of myocardial perfusion quantification produced an extensive and technically robust literature, with over 250 papers including almost 15,000 subjects in the past 25 years' (p. 1640).[4] Looking into this literature to exactly see 'how much'—the Latin '*quantus*' of the word quantitative'—we might not find the definitive answer. Reported hMBF values for the healthy normal volunteers can have as low values as 1.50 ± 0.74 mL/min/g[5] and patients with established CAD—as high as 3.18 ± 0.85 mL/min/g,[6] both studies done with ^{13}N-ammonia. And the range of MFR cutoffs in the four ^{13}N-ammonia papers authors pooled—1.83 to 2.40—though substantial is not that large as the one existing in the literature—1.44[7] to 2.74.[8] Ranges for hMBF are wide too. Looking at the ranges (of note, with ^{15}O-water the range is less spread),[9] one might wonder how metrics, widely used to determine the diagnostic path of a patient, can have such a wide range—cutoffs having a double difference and values in healthy and sick largely overlapping.

To understand that, first, we may have to accept that different tracers may behave differently in quantification and may need different cutoff values. Second, PET

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instrumentation can harbor certain sources of precision and accuracy error; here, one can reasonably argue that technology advances and numbers that we get in 2018 are more accurate than those received in year 1988. Likely so, but does it practically mean that we should discard all the earlier results? What year should be the 'cutoff' year? Third, we must remember that the basis of all the quantification in PET is the transformation of the measured radioactivity concentration values into milliliters of blood per minute per gram of myocardial tissue (mL/min/g). This process is done in and with PET software tools, and consists of several steps, each of which can affect the results. These issues are reviewed at large elsewhere.[10] In the study of Sang-Geon Cho et al,[1] the analyzed papers utilized four software tools—CardiacVUer, Carimas, FlowQuant, and PMOD—however, there are more. We have demonstrated[11] on Rb-82 PET and ten software tools that results they provide can differ twice or even more. To summarize, the PET cardiac analysis field now exists in a fragmented state with many players—commercial developers, non-commercial developers, and units only producing software tools for themselves. Thus, it is possible that any established cutoff would only be meaningful for the particular software used to establish it. Consequentially, pooling of results might not be that useful. What then?

There might be three ways: the first is that 'each PET facility has to establish its own flow values indicating ischemia' (p. 1646).[4] It is indeed possible to build an all-inclusive custom system from a PET scanner to the analysis software, which will provide the robust results in that facility; yet, it undoubtedly leads to compartmentalization of nuclear cardiology as it prevents communication of results between the facilities as well as the possibility to pool the results from several centers. The second is to find a common denominator for the existing tools. In practice, it means the following: it is not currently feasible to single out 'the one' software solution, make everyone let go the tools they have been using for years already, and switch to that one tool. What is feasible, however, is to test all the tools on common datasets, find out where each of the tools stands in respect to the rest, and use these results in pooling and communicating the data. This way has its pitfalls—version control being one of the prominent. And the third, which we currently think is the best—to enable the emergence of a single tool, which would be developed by the community and would be free for all. We think that before the emergence of a single, widely adopted, tool, getting to a higher level of understanding in the field is hardly possible.

The general researcher's statement '*we found that parameter P has value V*' can advance knowledge if we are solid about this *V*; otherwise, having received its share of citations, it gradually melts with thousands of indistinguishable statements and disappears. In our opinion, we cannot be that solid about the values received by Sang-Geon Cho et al[1] However, the work they present is an important undertaking that can lead to the discussion on how accurate we are when presenting numbers with two or even three digits after the decimal point—the discussion that is long-awaited in our field.

Disclosure

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