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EDITORIAL COMMENT

Coronary CT Angiography With PET Perfusion Imaging

Hybrid or Hype?*

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In this issue of *iJACC*, Maaniitty et al. (1) provide real-world outcomes data resulting from their hybrid imaging strategy combining coronary computed tomography angiography (CTA) with quantitative cardiac positron emission tomography (PET). Their findings provide an ideal opportunity to revisit existing European guidelines on hybrid imaging (2): Class III ("is not recommended") for all patients except Class IIa ("should be considered") for those with symptoms and a 15% to 85% probability of "significant" disease.

NEW DATA FROM TURKU

The new results report outcomes of all-cause death, myocardial infarction (MI), and unstable angina in a retrospective study of 864 patients (1). When the coronary CTA showed a visual ≥50% diameter stenosis, quantitative PET perfusion using oxygen-15 (O-15) with adenosine stress was carried out because the authors note that coronary CTA alone has a low specificity for significant coronary artery disease (CAD). Approximately one-half of the patients had nonobstructive CAD by coronary CTA; and of positive coronary CTAs, approximately one-half had abnormal PET perfusion (defined as global stress flow ≤2.4 cc/min/g in 1 or more of 17 segments).

Adverse events at median of 3.6 years occurred in 0.4% of patients with normal coronary CTA, 0.5% with stress perfusion >2.4 cm^3/min/gm, 1.5% in patients with positive coronary CTA, and 2.5% in patients with global perfusion ≤2.4 cm^3/min/g that the authors emphasize was 5 times the rate in patients with normal perfusion.

THE STRONG, MAJOR CONCLUSION

The authors are to be congratulated for demonstrating feasibility of a technically challenging sequence of upfront coronary CTA with one-half of patients then receiving O-15 cardiac PET stress perfusion imaging, all within 30 min and at a cost reportedly comparable to single-photon emission computed tomography. The key message of this study confirms physiology over anatomy for assessing physiological severity of CAD to predict major adverse cardiovascular events (MACE). Indeed, the authors make this physiological victory explicit: "statistically significant predictors of adverse events (AEs) were increasing age and abnormal perfusion by PET" with an "annual rate of AEs … 5 times higher in patients with abnormal perfusion compared to patients with a normal PET perfusion study (2.5% vs. 0.50%; p = 0.004)."

PARADOXICAL INSTRUCTIVE WEAKNESS

However, paradoxical weaknesses teach equally important lessons. Despite the authors' own data, they express reluctance in the discussion to embrace physiology over anatomy. Furthermore, they propose a straw-man alternative of the "unselected performance of both tests to all patients" instead of

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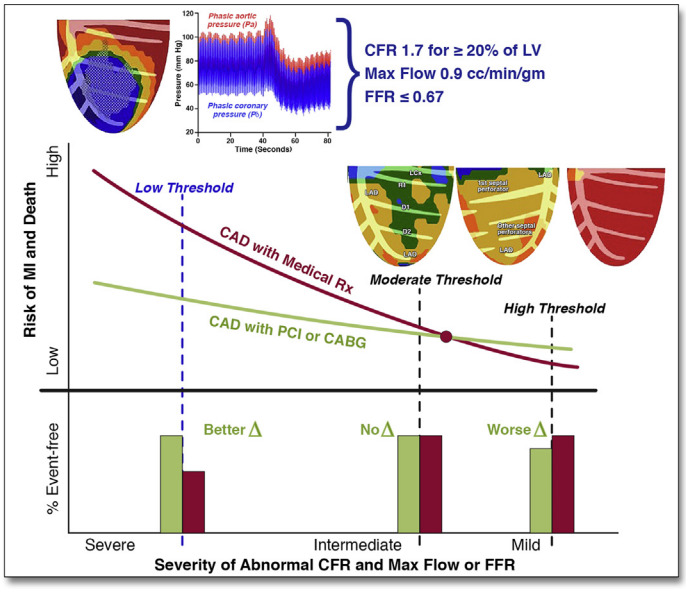
FIGURE 1 Threshold of Physiologic Severity in CAD



The physiological severity threshold at which revascularization improves event-free survival more than the risk of the procedure occurs at the intersection of severity versus risk curves shown by the **red dot**. PET image inserts with color scale of coronary flow capacity including high for young healthy volunteers **(red)**, minimally reduced **(orange)**, mildly reduced **(yellow)**, moderately reduced with either electrocardiographic changes or angina or regional dipyridamole stress defect **(green)**, and severe **(blue)** with angina, ST change, and regional stress defect during dipyridamole stress. Reprinted with permission from Gould and Johnson (6). CABG = coronary artery bypass graft; CAD = coronary artery disease; CFR = coronary flow reserve; FFR = fractional flow reserve; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LV = left ventricular; MI = myocardial infarction; PCI = percutaneous coronary intervention; Rx = prescription.

addressing the essential scientific question—why not just PET alone because it predicts outcomes and, as the authors themselves write, "because functional information is currently used as the main criterion for the revascularization decisions"?

WHY NOT JUST PET?

An initial PET without coronary CTA would further reduce radiation, shorten diagnostic time even more, predict MACE, and guide interventions as affirmed by their own data. The authors pose this possibility in their discussion: "another option would be to start with perfusion imaging." The 3 components of their reluctance bear critical examination:

- "The drawback of this approach is that some nonobstructive atherosclerosis will be missed."
- "Performing coronary CTA first reduced the need to do the PET perfusion study."
- "As anatomical data are acquired from every patient, this information can be used to guide the pharmacological therapy."

Because quantitative PET clearly identifies diffuse CAD (3) underappreciated by coronary angiography, because risk factors need treatment according to guidelines, and because PET predicts MACE and guides interventions in their own lab, why is it important to reduce PET that is "fast" at their center and "no more expensive than SPECT"? Notably the current study does not prove that a coronary CTA-PET sequence is better than PET alone because there is no PET only group and hence no support for added value of coronary CTA.

IMPROVED ACCURACY WITH HYBRID CORONARY CTA AND PET?

As described in Danad et al. (4), "On a per-patient basis, the sensitivity, specificity, negative predictive value, and positive predictive value of CTCA were 100%, 34%, 100%, and 51%, respectively, as compared with 76%, 83%, 83%, and 76%, respectively, for quantitative hyperemic MBF PET." The authors argue that the 100% sensitivity of coronary CTA serves to avoid missing significant CAD. Additionally, its low specificity of 34% that would produce too many false positives is partially compensated for by the 83% specificity of O-15 PET, thereby improving accuracy. In other words, the authors' view is that the accuracy of hybrid coronary CTA-PET is better than the accuracy of either coronary CTA or PET alone.

Danad et al. (4) also state that "because $H_2{}^{15}O$ water is metabolically inert and freely diffusible, signal-to-noise ratios and contrast between tracer concentration in the blood and in the myocardium is low, compared with other perfusion tracers such as ^{13}N-ammonia and ^{82}Rb." Despite this disadvantage, recently presented data show that O-15 quantitative PET offers the same diagnostic performance as hybrid coronary CTA plus PET (5); compared to the standard of FFR, the accuracy of PET alone was 85% and not improved by adding coronary CTA with hybrid accuracy of 84%.

3 OTHER IMPORTANT LESSONS FROM THIS STUDY

First, the authors conclude that "there was no difference in annual rate of AEs or all-cause mortality between revascularized or nonrevascularized patients (2.1% vs. 2.8%, p = 0.57; and 0.52% vs. 1.5%, p = 0.17, respectively)." These results parallel all prior

randomized revascularization trials analyzed by classical intention to treat that showed no significant improvement in event-free survival or reduced coronary events after revascularization compared with optimal medical treatment.

Rather than negating revascularization, we editorialists explain this counterintuitive result of randomized trials as being due to selecting patients with physiologically mild-to-moderate coronary disease for whom the risk of the disease is no higher than the risk of the revascularization with a resulting lack of benefit (3), illustrated in **Figure 1** (6). In the current report, the high coronary flow reserve (CFR) threshold of 2.4 associated with low MACE rates in patients with CAD reinforces the message of **Figure 1**.

Second, the PET perfusion threshold for ischemia appears too high for optimal risk stratification. Several statements made by the authors support this view: "Studies in large populations have also shown that the presence of nonobstructive atherosclerosis has prognostic significance." "However, in the present study we could not observe this"; "the annual rate of all combined AEs was 0.95% and the annual rate of all-cause mortality was 0.54%"; and "the annual rates of all-cause mortality in patients with reduced perfusion and in patients with normal perfusion were 1.07% and 0.38%, respectively. The difference was not statistically significant ($p = 0.12$)."

One explanation for these results is a CFR threshold set too high at 2.4 because the literature reports that a much lower CFR threshold of 1.5 is necessary for significant MACE (7) or definite ischemia (8). Moreover, in the current study, the threshold for size is also too small ("at least in 1 of the 17 myocardial segments"). As a consequence of this high CFR threshold for small areas (1 of 17 is <6% of the LV), many patients with low risk were included as "abnormal," thereby diluting the predictive value for MACE.

Third, old habits die hard, as evidenced by the statement, "In the initial interpretation of coronary CTA, ≥50% diameter stenosis by visual analysis was used as a criterion for suspected obstructive stenosis." An extensive literature documents this visual sorting of disease severity as deeply flawed for scientific or clinical purposes since it is insufficiently related to physiological severity (9).

CONCLUSIONS

We editorialists return to the great strength of this important paper by an expert group confirming that coronary physiology determines the fate of our hearts, not its hyped hybrid with anatomy.

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