The judgement of the eye

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Received Jan 8, 2016; accepted Jan 8, 2016
doi:10.1007/s12350-016-0412-8

BEAUTY IS BOUGHT BY JUDGEMENT OF THE EYE¹

The point-counterpoint of Saab et al, and Reynes et al^{2,3} is very well done and reminiscent of the Mirror of Erised of the Harry Potter series in which one sees their desire while gazing into it. Both make compelling arguments on the impact of caffeine ingestion on the accuracy of SPECT myocardial perfusion imaging. Both quote from the same studies, yet see opposite but credible conclusions. Clearly, there is a literature supporting an inhibitory action of caffeine-containing products on coronary vasodilation mediated by adenosine A2 receptors but the timing, dosage, vasodilator agent, and specific genetic predisposition to caffeine variability clouds the looking glass. The first description of caffeine impact on dipyridamole-mediated vasodilation was in 1989.⁴ Twenty-five years later, the impact of the issue is still uncertain. Why are we not further along? This piece will outline some concepts that have contributed to the confusion. These are within the categories of imaging algorithms, image displays, physics, tracer kinetics, and statistics.

TEMPORAL REPRODUCIBILITY

Most of the small studies exploring the impact of caffeine on vasodilation rely on serial perfusion imaging studies. While inter- and intra-observer variability for interpreting SPECT perfusion studies has been fairly well defined,⁵ temporal reproducibility has not. Despite common clinical utilization of prior perfusion studies to detect changes in the coronary circulation over time in patients, there are limited data on the reproducibility of such comparisons by SPECT imaging.⁶ Consequently, it is hard to interpret vasodilation perfusion studies of

small sample size, performed with and without caffeine on board, as there is not a clear quantitative threshold by SPECT imaging that constitutes a significant change. If there was a standard quantitative methodology, the confidence in determining a serial change between studies would be greater.

MYOCARDIAL MODELS OF MYOCARDIAL PERFUSION VARY

Another confounder is the use of segmented myocardial perfusion models. These truncate the ability to detect changes that are spread over two segments, diluting the difference. This can be a limitation. Another is the use of the summed stress and rest scores which tabulates all hypo-perfused segments on the images. The 17-segment perfusion model is the clinical approach that is relevant due to its widespread adoption despite shortcomings. While the summed stress score is widely used for clinical interpretation of images, a disadvantage is the mixing of reversible viable segments with fixed nonviable segments. This method is present in a number of the studies cited by the authors. If caffeine has a clinical impact on perfusion images, it will be found only in the viable segments. Nonviable segments will not take up conventional SPECT perfusion agents despite the presence of blood flow. The summed stress score mixes these together. Limiting the analysis to the reversibility score avoids the confusion. Several studies referenced have used a measure of defect size as a continuous variable (area of the LV) which should be able to detect more subtle changes. This is a better approach but, as we will see, the relative nature of perfusion imaging can make any serial image comparison problematic.

ABSOLUTE VS RELATIVE MYOCARDIAL BLOOD FLOW

Another confounding factor is the use of relative myocardial blood flow (MBF) algorithms for image reconstruction. Three small studies have shown a

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J Nucl Cardiol 2016;23:454–6.
1071-3581/\$34.00
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Figure 1. Potential probability curves estimating the impact of caffeine ingestion on vasodilation perfusion SPECT imaging from three papers cited by the discussants.^{11,13,14} The height of the curve is a reflection of the sample size with the peak corresponding to the mean probability estimate of the impact of caffeine on SPECT clinical imaging, and the width reflecting the confidence interval of the prediction. Each curve is cumulative from the previous such that the final curve includes probability estimates from that study plus the estimate of the impact of the two prior studies combined. These curves are hypothetical only and not accurate reflections of a Bayesian analysis.

decline in absolute MBF (least pronounced when regadenoson was used as the vasodilating agent) in the presence of caffeine as assessed by PET perfusion imaging.⁷⁻⁹ But this does not necessarily translate to a change in perfusion imaging using SPECT techniques. Because of the lack of an arterial input function for most protocols and significant attenuation and scatter, SPECT imaging is not amenable to quantifying absolute MBF. Alternatively, a relative signal intensity algorithm is necessary to compare images by bringing up the maximum signal intensity to maximal brightness within each image. This region can vary between studies and limit the ability to recognize a decrease in vasodilation as the serial images are of equal signal intensity in at least one zone. There is no reason not to assume that stress flow in normal and abnormal flow reserve zones will not be reduced equally, thus limiting the ability to detect a decrease in vasodilation by caffeine. Consequently, we are left deducing whether caffeine is impacting vasodilation by a decrease in defect reversibility in zones supplied by diseased arteries rather than by simply measuring MBF in the myocardium.

ROLL-OFF UPTAKE KINETICS OF SPECT PERFUSION AGENTS

Early work on both Tc-99m-isonitrile tracers and Thallium-201 demonstrates that uptake of these perfusion tracers is linear at lower flow rates but plateaus at

MBF values of 2.0-2.5 ml/minute/g.¹⁰ Vasodilator stress increases MBF to 4.0-5.0 ml/minute/g in normally perfused myocardium. No SPECT tracer can reflect that level of MBF. The three absolute MBF studies quoted in the pro and con articles⁷⁻⁹ show MBF vasodilation values without caffeine ranging from 2.97 to 4.11 ml/minute/g and with caffeine of 2.25-2.75 ml/minute/g. All of these values are at or higher than the uptake plateau flow rate. Consequently, it may not be possible to consistently show an impact of caffeine on MBF vasodilation using SPECT tracers.

FREQUENTIST VS BAYESIAN STATISTICS

The approach of both discussants regarding the clinical literature is to treat each study independently. Consequently, there is no relationship between prior studies and no common thread to tie them together. In such an approach, sample size becomes important and randomized trials (of which there is one¹¹) become critical. This is known as a frequentist approach to scientific analysis. I would argue that this approach does not work here because of the small sample sizes and variability in design between studies. Rather a Bayesian approach would provide more clarity.

In a frequentist approach, any knowledge or evidence available prior to the measurement period is not used to generate conclusions, although it may be incorporated into the study design. In addition, the required sample size for the control and treatment

groups needs to provide a result that will stand on its own statistically; a treatment will either be deemed effective at a statistically significant level, or it will not.

In contrast, the Bayesian approach does use prior knowledge or evidence to generate conclusions. The theorem asks, “What is the probability that a new result is providing a true estimate of the effect in question given the evidence accumulated to this point?” In other words, the likelihood of getting a particular result from a clinical trial, formally known as the posterior probability, depends on the findings of the trial itself as well as the pre-trial probability of the results of all the previous studies to date, formally called the prior probability distribution. Each study provides an estimate of the true impact of caffeine on MBF with a confidence interval for that prediction that can be analyzed as a cumulative variable.¹² We could order these chronologically and establish a prior probability after each study is added, so as to derive the cumulative probability estimate based on all the data. Studies can be weighted by sample size and strength of design. A hypothetical graphic of that approach is shown in Figure 1.^{11,13,14}

Bayesian analysis places the accumulated data in perspective with a final estimate of the impact of caffeine on MBF with a confidence interval of that estimate. This could be done with the studies cited in the arguments for the impact of caffeine ingestion prior to vasodilation stress. In the absence of that, looking at the data using an eyeball approach, it looks like the confidence interval regarding the impact of caffeine still crosses 1.0 but is leaning toward the impact side. But leaving it to the eye allows beauty to be judged subjectively. A large randomized trial could settle the issue using both absolute MBF with PET and serial SPECT imaging with a defined reproducibility threshold that must be eclipsed for significance and a standardized protocol. But we should not lose sight of the good prognosis associated with a normal myocardial perfusion study, most recently confirmed with regadenoson vasodilation.¹⁵ Events are rare. Consequently, it is not likely that there is a large cohort of coffee drinkers with falsely negative vasodilator perfusion studies out there. A better approach might be to direct effort and resources into lower cost laboratory quality metrics aimed at preventing patients from ingesting caffeine prior to testing. Then the eye can focus on the judgement of the images.

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