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EDITORIAL COMMENT

Dynamic Stress Perfusion CT

2 Out of 3 Ain't Bad?*

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I want you, I need you
But there ain't no way I'm ever gonna love you
Now don't be sad (don't be sad)
Cos two out of three ain't bad.
—Meatloaf (1)

Quantitative assessment of organ blood flow by computed tomography (CT) is not a new goal. Ironically, it was Leon Axel (2)—later much better known for his work in the field of cardiac magnetic resonance (CMR) imaging—who was among the first to suggest the theoretical basis for achieving this in his 1980 paper on quantitating cerebral blood flow following cerebrovascular events. Subsequently, Ken Miles and Adrian Dixon (3) from Cambridge, United Kingdom, demonstrated the feasibility of tissue-level parametric mapping of blood flow. Initially, the application of this technique to the heart seemed challenging, given the temporal and spatial requirements for adequate coverage. However, rapid advances in scanner technology, combined with the curiosity of the cardiovascular CT community, has led to growing interest in functional CT imaging of the heart. In theory, myocardial CT perfusion (CTP) might be regarded as the perfect partner for CT coronary angiography (CTA)—the holy grail of anatomy and perfusion, perfectly coregistered, the ultimate standard of reference. In practice, CTP has been largely overlooked in the headlong rush toward computational methods for deriving coronary physiology. The reasons are varied but include: 1) a reasonable concern about radiation dose; 2) an unwillingness to prolong examination table time in busy institutions; 3) a reluctance to employ vasoactive drugs, particularly in some departments; 4) a lack of software tools for analyzing CT perfusion images; and 5) an uncertainty about which of the published perfusion protocols to employ. This last point is particularly pertinent because the term *perfusion* has been used rather loosely in the cardiac CT published reports. In essence, perfusion refers to flow of blood as a function of time. This obviously requires a dynamic acquisition with the sample volume being re-imaged at short, evenly spaced intervals following injection. However, a number of studies with "perfusion" in the title are instead describing imaging at a single fixed time point shortly after contrast injection—a technique that might be more accurately described as iodine mapping rather than perfusion.

STUDY POPULATION

In this issue of *iJACC*, Nakamura et al. (4) employed dual-source technology and rapid shuttle mode to acquire genuine time-resolved datasets under vasodilator stress, together with a single time point acquisition at rest for coronary anatomy. The aim of the study was to compare CTA alone versus a combination of CTA and CTP for medium-term outcomes. Considered for inclusion were a retrospective population of 625 consecutive patients who were referred for CTA/CTP at a single institution. As in most cardiology studies, the majority were male (and presumably, though not stated, monoethnic). Regrettably, the mean body mass index was not provided; this would have been helpful to assess the generalizability of the CT technique employed (see the following text).

TECHNIQUE

Several points regarding the technique used are due consideration. The choice of stress agent, adenosine triphosphate (ATP) may be unfamiliar to Western physicians but is commonly employed in the Far East for nuclear perfusion imaging. As the precursor to adenosine, it has very similar vasoactive effects (and

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side effects) but is usually given at the slightly higher dose of 160 μg/kg/min, with tracer agent (in this case iodine) given at 3 min but with continued ATP infusion post-tracer injection for at least a further 2 min (for single-photon emission computed tomography imaging) (5). In this study, ATP was discontinued once image acquisition was complete, presumably 30 to 40 s after contrast injection. It is unclear, therefore, whether maximal coronary dilatation could have been achieved in this time period, which likely was <4 min in total.

Secondly, the authors report the use of 70 or 80 kV for the CTP portion of the protocol. This results in an acceptable dose but at the risk of introducing unacceptable levels of noise, especially in larger patients. Because the body mass index of the subjects is not provided, it is difficult to assess the applicability of the technique to other populations outside of Japan, which has an obesity rate of only 7% compared with 27% in the United States (6).

Thirdly, quantitative rather than qualitative (visual) measures of perfusion were employed. Although intuitively attractive, one CMR study that addressed this found no added diagnostic benefit over a purely qualitative read (7). The authors could not generate a measurement of perfusion reserve comparing hyperemic to resting flow—as is conventionally done in CMR and positron emission tomography imaging—because they did not acquire time-resolved images in the resting state (presumably to reduced total radiation burden). Instead, they used mathematical modelling to estimate values of absolute myocardial blood flow from the stress series alone. They then normalized the blood flow value per segment to the highest flow (i.e., the most normal segment) anywhere within the 17-segment model. The need for normalization is not spelled out in the paper but presumably reflects a need to average out noise within the data. The presence of noise in the system is demonstrated by the fact that in patients without obstructive disease, the lowest ratio of segmental to global perfusion was not 1.0—as might be expected under perfect conditions—but instead was 0.75. Scaling to the most normal value in this way opens the door to the possibility of underestimating ischemia in the presence of triple vessel disease if there are no segments with normal perfusion. As such, the authors risk diluting the benefits of using a quantitative method in the first place. They then generated range categories for normalized stress perfusion and created a 17-segment summed stress score based upon the point value assigned to each of the categories. With the exception of the cutoff used to define normal (>0.75), it is unclear how the remaining thresholds were determined and whether they were decided upon a priori, a pertinent consideration when reviewing the subsequent Kaplan-Meier event curves.

RESULTS

After exclusions (due to prior percutaneous coronary intervention/coronary artery bypass grafting/myocardial infarction), 332 patients with suspected coronary artery disease remained in the study. The fact that only 10 patients were excluded due to image artifacts is encouraging, but may reflect the likely low mean body mass index of their patients by North American and European standards. Mean total dose was a little over 7 mSv, which is quite reasonable for this kind of protocol; whether this could be reproduced with acceptable image quality in a heavier population is debatable. Only 28% had an abnormal perfusion study (defined as a summed stress score [SSS] >4), and only 6% had a severely abnormal study (SSS >12). Thus, the overall presence of obstructive disease, defined by perfusion, was low, which is problematic when looking at relatively short-term endpoints (median follow up 2.5 years, upper bound around 4 years), borne out by the fact that none of the conventional major coronary risk factors were associated with a significant hazard for major adverse cardiac events (MACE), even in univariate analysis, due to the short duration of follow-up. Nonetheless, the authors were able to show a significant difference in combined MACE between those with a SSS >4 (abnormal perfusion) compared with those with a SSS <4 (normal perfusion). When considering only hard endpoints (death, nonfatal myocardial infarction), the difference was reduced but remained statistically significant, although with a total of only 5 hard outcomes, the clinical significance remains open to question. Statistical limitations include the possibility of nondifferential loss to follow-up, as well as death from competing risks, which if censored, tends to inflate the cumulative incidence frequency and artificially accentuates differences between groups, therefore requiring a different modelling approach (8,9). Even assuming that competing risk was not an issue, the confidence intervals surrounding the hazard ratios for MACE from their Cox proportional hazards modelling of abnormal perfusion in varied scenarios are sufficiently wide to suggest they should be interpreted with appropriate caution.

WHY SHOULD WE STILL STRIVE FOR CT MEASURES OF ISCHEMIA?

Even the most ardent enthusiast of cardiac CT would admit to its limitations. However, so many advances have been made in vendor technology, dose-reduction, temporal resolution, reconstruction

algorithms, and post-processing software that the claim that cardiac CT is "a step backward" (*JACC* editorial, 2008 [10]) seems unduly harsh a decade later. Yet, several of Nissen's criticisms undoubtedly still ring true to our ears (8). Despite excellent negative predictive value, every reader will have experienced the frustration of trying to interpret intermediate lesions or deciding whether there is simply too much calcium to be able to "read through." The positive predictive value for obstructive disease is variable in trials run by the world's experts and may be even lower in real life (11–13). Intravascular ultrasound studies have taught us that we routinely underestimate luminal area and that interobserver variability for the same lesion is wide (14). Perhaps more importantly, trials such as CECaT (Cost-Effectiveness of Noninvasive Cardiac Testing) (15,16), DEFER (17–19), FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) (20,21), and FAME 2 (Fractional Flow Reserve [FFR] Guided Percutaneous Coronary Intervention [PCI] Plus Optimal Medical Treatment [OMT] Versus OMT) (22) have repeatedly demonstrated that ischemia-driven management is as effective as, or often more effective than, management decisions based upon luminography alone (23).

As a result, cardiac CT ischemia research has effectively branched in 2 different directions: stress perfusion imaging and CT-derived fractional flow reserve (CT-FFR) (24,25). Currently, most research efforts are focused on the latter (aided by industry financing) with several encouraging trials having shown improved diagnostic accuracy compared with CTA alone, even if the positive predictive values remain lower than one might wish (26–29). Furthermore, data from the PLATFORM study (Prospective LongitudinAl Trial of FFRct: Outcome and Resource IMpacts) suggest that a CT-FFR-guided strategy is associated with equivalent outcomes and lower costs at 1 year compared with an invasive angiography strategy (30). However, the technique remains limited to some degree by motion and image misregistration, although, counterintuitively, coronary calcification does not seem to significantly affect accuracy (31,32). Also unclear is whether CT-FFR analysis—which is currently provided off-site commercially by a single company—will be able to upscale operations quickly enough to cope with the significant increase in volume expected since Medicare approval of the technique at the start of 2018 (33). In the longer term, vendor-provided equivalent solutions at point of care will surely be required.

With so much enthusiasm for deriving physiology from CT, why has CTP failed to make more of an impact? The reasons are multifactorial. Table time is limited in most hospitals, and fitting in stress studies may be difficult without knowing in advance whether the coronary anatomy will require this, especially because a wash-out period for contrast is required between the 2 portions of the study. Radiation dose is another major concern and the dominant reason why single time point rather than dynamic CTP acquisition protocols have prevailed. Perhaps most importantly, CTP was unlucky to arrive at a time when the zeitgeist favored computational approaches to identifying ischemia. These factors (together with industry sponsorship of research in FFR-CT) have left CTP the awkward uncle at the wedding. A recent meta-analysis of published papers on (human) static CTP found fewer than 1,200 patients, albeit with evidence that CTP improves specificity compared with CTA alone (34). The published reports for dynamic CTP are even more limited and have been dominated by a few centers with dual-source technology. Mostly these studies have focused on accuracy, although one multicenter registry publication did look at prognostic ability, and showed, similar to Nakamura et al. (4), that visually appreciated perfusion defects provided additional prognostication even after adjusting for CTA findings and that the hazard for MACE was strongly related to the number of abnormal segments (35).

SO, 2 OUT OF 3 AIN'T BAD?

There is a clear argument that CT needs to provide physiological assessment, but there is a dichotomy appearing in the published reports as to how to do this best and most cost-effectively. Nakamura et al. (4) are to be congratulated for their efforts, and their work represents an important contribution to the existing published experience with dynamic CTP. Whether prognostication is what drives the hand of the referring physician when choosing between tests is another matter. For CT perfusion to be accepted longer term, there needs to be much more work done on harmonization of protocols and prospective multisite multivendor comparisons of static versus dynamic CTP methods—with a primary focus on diagnosis and a (still important but) secondary focus on prognosis. We want and need CT perfusion, but whether ultimately it will prove to be a flirtation or a lasting love affair remains to be resolved.

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