

Coronary flow reserve by CT perfusion

Richard T. George, MD,^a Frank M. Bengel, MD,^b and Albert C. Lardo, PhD^{c,d}

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Cardiovascular computed tomography (CT) is one of the most impressive advances in the non-invasive diagnosis of cardiovascular disease in the last decade. Going beyond coronary calcium scoring, cardiovascular CT is capable of identifying calcified and non-calcified plaque, percent stenosis, cardiac structure and morphology, and left ventricular systolic function. The abilities to detect subclinical and obstructive atherosclerosis and exclude disease with high diagnostic certainty are its greatest attributes. Single-center and multi-center studies in various cohorts have established that CT coronary angiography (CTA) is an accurate non-invasive test for determining percent stenosis which can be performed with low radiation dose.¹⁻⁷ However, it is important to point out that coronary CTA is an anatomical test that does not provide important physiological data. In fact, the value of CTA for predicting the presence of myocardial ischemia is limited.⁸⁻¹⁰ While coronary CTA has an excellent negative predictive value, it is more limited in determining the significance of stenoses in patients with disease. Thus, caution needs to be exercised when adopting cardiac CT clinically. The importance of coronary physiology for diagnosis, prognosis, and guidance of therapies must not be ignored.

Invasive measurements such as fractional flow reserve have been shown to impact outcomes in patients with coronary stenoses and guide the appropriateness of invasive therapies such as intracoronary stenting.¹¹⁻¹³ Radionuclide myocardial perfusion imaging is an established diagnostic tool for detecting obstructive coronary

artery disease and is proven to accurately predict prognosis and guide therapy.¹⁴⁻¹⁶ Furthermore, it has been shown to add incremental prognostic value above and beyond what is provided by invasive angiography.¹⁷

While the major focus of cardiac CT research has been its application in coronary angiography, our group and others have recognized that X-ray computed tomography using iodinated contrast as a tracer is capable of providing measurements of myocardial blood flow and blood volume.^{8,18-20} In this issue of the *Journal of Nuclear Cardiology*, Christian and colleagues use the upslope integral method, a previously described method published in the magnetic resonance perfusion imaging literature, to demonstrate cardiac CT's potential to quantify coronary flow reserve (CFR) independent of the arterial input function.²¹ In summary, they performed dynamic CT perfusion imaging in a canine model that received intracoronary adenosine in one vessel supplying a hyperemic territory, while the remote territory was kept at baseline conditions. In addition, several experiments employed CT perfusion imaging during temporary occlusion of a vessel. Images were analyzed by measuring the attenuation changes over time in the remote and hyperemic territories and plotting time-attenuation curves. They then calculated the area under each myocardial curve during the upslope to peak of contrast enhancement and calculated CFR by taking the ratio of area under the curve for the hyperemic territory and the area under the curve for the remote territory.

The reported results are quite impressive. Compared to the gold standard, CT-derived CFR showed an excellent correlation with microsphere-derived CFR ($r^2 = .9325$). There was also an excellent agreement between CFR by CT vs microspheres, 4.4 ± 1.4 vs 4.1 ± 1.1 , respectively, with 95% confidence limits of difference between the measures of 1.08. This study demonstrates that CFR can be accurately derived from CT. The authors suggest that this method could be implemented by setting the highest slope integral value as a normalization standard and calculating CFR relative to this normal value. They postulate that this could be performed with as few as 5 heart beats and independent of the arterial input function, while also acquiring the CT angiogram using a single contrast bolus and scanning session. While these preclinical results look promising, the implementation of this method faces several technical challenges.

From the Department of Medicine, Division of Cardiology,^a Russell Morgan Department of Radiology, Division of Nuclear Medicine,^b Department of Medicine, Division of Cardiology,^c and The Department of Biomedical Engineering,^d Johns Hopkins University, Baltimore, MD.

Reprint requests: Richard T. George, MD, Department of Medicine, Division of Cardiology, Johns Hopkins University, 600 N. Wolfe Street, Carnegie Building 565C, Baltimore, MD 21287; rgeorge3@jhmi.edu.

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First of all, the value of determining CFR using quantitative methods in magnetic resonance (MR) and positron emission tomography (PET) is in determining the increase in myocardial blood flow from resting to stress conditions. This requires calculating myocardial blood flow in absolute terms during rest and stress. This allows, in quantitative terms, the capability of looking beyond relative differences in myocardial perfusion and examining the blunted response to a hyperemic stimulus in the setting of obstructive coronary artery disease. The calculation of CFR allows more accurate diagnosis in the setting of multivessel coronary artery disease and offers the capability to detect early changes in asymptomatic patients with subclinical disease.²²⁻²⁴ However, the quantification of coronary flow reserve from myocardial blood flow calculations derived from rest and stress imaging requires an accurate characterization of the arterial input function since this will change between rest and stress conditions. In the present article, rest and stress conditions were created simultaneously using selective infusion of adenosine to one territory and comparing this to the remote territory. This created the opportunity for rest and stress imaging during the same contrast bolus (i.e., arterial input function) and avoided differences in arterial contrast transit times seen under rest and stress conditions. Unfortunately, this experimental scenario is only possible in patients if performed during coronary catheterization with intracoronary adenosine and not possible during an infusion of iodinated contrast through a peripheral vein. Therefore, measurement of CFR in the traditional sense, stress MBF/rest MBF, is not possible using this technique.

This method, however, does allow for the calculation of a relative CFR during vasodilator stress. This requires that there be a territory that has completely normal perfusion to be used as a reference standard. In the setting of single vessel disease, a CFR could be calculated in the abnormal territory compared to the normal territory. To enable this in patients, either wide-detector arrays with 320 detectors or, in the case of narrow detector arrays (64-128 detectors) “shuttle” mode protocols are required.^{25,26} In addition, implementation of this technique would require real-time bolus tracking that was capable of detecting the arrival of contrast in the myocardium, immediately changing to full dynamic volume imaging, and terminating imaging at the peak of contrast enhancement. Unfortunately, one can see how this method would fail in the setting of multivessel disease where there is no normal reference and in patients with normal global perfusion since the CFR calculated by comparing one territory to another would be equal to one. Furthermore, it should be noted that flow reserve in patients with coronary artery disease

may be impaired in “remote” territories that are not supplied by a stenotic epicardial artery.²⁷

The authors have well demonstrated that dynamic CT is capable of accurately measuring changes in contrast enhancement over time and that these changes in contrast enhancement do, in fact, accurately reflect physiologic changes in MBF. This article, as well as others, also confirms that important differences in myocardial perfusion can be detected during the upslope to peak of contrast enhancement.^{18,19,28} Iodinated contrast is a diffusible tracer that distributes in the intravascular and extracellular space. Therefore, it is important to image the tracer at a time when attenuation in the myocardium represents perfusion instead of diffusion. Furthermore, CT attenuation measurements in the myocardium reflect a combination of iodine content in the arterial, capillary, and venous systems. Therefore, imaging early during the upslope of the contrast enhancement curves allows measurements to reflect arterial perfusion. Lastly, restricting imaging to the upslope of the time-attenuation curves allows protocols to minimize radiation dose while acquiring the most important CT perfusion data.

Validation of adenosine stress perfusion imaging using multi-detector CT in single center clinical cohort studies has primarily focused on imaging a single point in time or over a short period of time during a contrast infusion.^{29,30} These studies have shown that CTA combined with CT perfusion imaging compares well with invasive angiography and SPECT myocardial perfusion imaging. The great advantage of this mode of imaging is that it can be performed with detector arrays containing ≥ 64 detectors and avoids the higher radiation dose from dynamic imaging. The disadvantage is that this type of imaging lacks information on the kinetics of contrast enhancement; although we have recently demonstrated that the arterial input function can be acquired using helical CT protocols.³¹ Our group has begun validation of adenosine stress CT perfusion imaging in the international multi-center cohort study CORE 320.

Dynamic CT perfusion imaging has been well validated in preclinical models of coronary ischemia. Going forward, there are several requirements for successful implementation of this method. First, radiation dose considerations are extremely important. Implementation of dynamic CT perfusion imaging would require limiting imaging to the shortest amount of exposure time possible. The current study provides insight into how this can be accomplished by targeting only the upslope of the myocardial attenuation curves. Reductions in radiation dose can also be accomplished using prospective ECG-gated protocols. However, due to adenosine-mediated tachycardia, CT perfusion imaging requires maintaining high temporal resolution. This can be accomplished using a 320-CT scanner with segmental

acquisition and reconstruction, or a dual-source CT. It is crucial to avoid motion artifacts that can interfere with the interpretation of CT perfusion images. Another strategy to reduce radiation dose is to use lower tube voltage and tube current; although, image noise needs to be considered. Secondly, contrast dose needs to be considered. If a CT perfusion study is performed in addition to a CTA, contrast dose could become a concern. As CT scanning systems become faster and can image the heart in a single heart beat or less, contrast doses have been reduced to as little as 50-60 cc for a wide-area detector scanner or scanners capable of high-pitch helical acquisition.^{26,32} Thirdly, beam hardening needs to be considered. Beam hardening artifacts interfere with the relationship between measured attenuation and iodine concentration and can cause significant errors in the evaluation of CT perfusion imaging. As a result, our group has recently validated a beam hardening correction algorithm capable of correcting for these artifacts and improving the relationship between CT perfusion metrics and absolute myocardial blood flow.³³

In conclusion, Christian and colleagues should be commended for the current study. They have presented a well-designed experiment that demonstrates the accuracy of dynamic CT perfusion imaging and the potential to measure coronary flow reserve. While translation of this method will require further technical innovation, they have continued to further validate the promise of this technology.

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