News and Views

Newer Methods for Noninvasive Assessment of Myocardial Perfusion

Cardiac Magnetic Resonance or Cardiac Computed Tomography?

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Nuclear scintigraphy is the most commonly used technique for assessing myocardial perfusion in cardiovascular medicine in 2009. However, the pendulum may swing toward newer imaging modalities over the next several years. Techniques with improved spatial resolution as well as speed of acquisition may be used with increasing frequency. One question that arises is, which technique will that be?

Eike Nagel, MD, PhD, makes an excellent case for cardiac magnetic resonance (CMR), discussing its high accuracy, the emerging data on prognosis, the powerful combination with late gadolinium-enhanced imaging of infarction, and relative safety, including freedom from radiation exposure. He readily points out the limitations at present for CMR which include the requirement for advanced training to be able to read through artifacts and the need for simplification of acquisition of the data on many of the modern platforms. The future of CMR lies in full quantification of myocardial blood flow.

João A. C. Lima, MD, and Richard T. George, MD, make the case for cardiac computed tomography (CT). The greatest strength of cardiac CT lies in its anatomic imaging of the coronaries with high spatial resolution and excellent negative predictive value. Combining perfusion data in studies with positive angiographic findings could cut down on the false-positive rate and improve overall accuracy in the combined examination. In addition, there are some patients with microvascular disease who may manifest abnormal regional perfusion despite absent epicardial stenoses. Limitations of the current technology include the high radiation dose necessary to do stress and rest studies. This problem may be overcome in the future with prospective gating and the advent of 256- and 320-detector row scanners.

For those cardiovascular imagers unsure of where the future may lie, please read on.

CMR Perfusion Imaging: The First-Line Imaging Technique?

Eike Nagel, MD, PhD

Perfusion is the answer. It is without much debate today that the pure visualization of the coronary artery lumen is insufficient for clinical decision making. The use of fractional flow reserve has been shown to be a
superior approach with better outcomes and reduced costs (1). Similarly, multiple studies have demonstrated that the absence of ischemia is a good predictor of event-free survival, and that the severity of ischemia is closely correlated to the occurrence of events (2,3). It seems to be important, however, to leave the concept of merely determining the presence or absence of ischemia and, rather, to move forward to determining the severity of myocardial ischemia. Clearly, any test to be used several times in life (for example, to assess recurring symptoms after treatment or remaining ischemia after initiation of therapy) or used to exclude disease to determine prognosis must be as minimally harmful as possible.

**CMR perfusion is highly accurate.** CMR perfusion imaging has now been widely validated and found to be highly accurate. In animal experiments, it has been shown to correlate well with microspheres and to be superior to single positron emission computed tomography (SPECT), most likely because of the higher spatial resolution of CMR perfusion imaging (4). Similarly, it has been validated against coronary flow reserve with a good correlation (with an r value of approximately 0.86). Comparison with fractional flow reserve resulted in a less favorable correlation. Classification of patients into normal or abnormal fractional flow reserve using CMR perfusion resulted in a sensitivity of approximately 90% with a specificity of approximately 90% in 2 studies, with a lower specificity (56%) in 1. Some differences to fractional flow reserve are to be expected, because coronary flow reserve is reduced in microvascular disease similar to CMR or cardiac CT perfusion imaging, whereas fractional flow reserve remains normal in these patients. The importance of these findings needs to be addressed in future studies. In several multicenter studies, the accuracy of CMR perfusion to determine coronary artery stenoses has been evaluated. The largest 2 multicenter multivendor trials are the IMPACT (Integrilin to Minimize Platelet Aggregation and Prevent Coronary Thrombosis) (5) and IMPACT II studies. In these trials, the superiority of CMR perfusion over SPECT for the prediction of an epicardial coronary stenosis was shown. Owing to the differences of the parameters measured (luminal stenosis versus myocardial ischemia), no 100% correlation between CMR perfusion imaging and the presence of a luminal stenosis can be expected. Prognostic value of CMR perfusion. To optimally guide therapy and decide whether to proceed to revascularization, it is more important to prove or exclude ischemia and predict the occurrence of events, rather than merely prove the presence of a luminal stenosis. Several studies have shown the high predictive value of CMR perfusion imaging for prognosis, both in the acute setting and for the chronic stable patient. A normal perfusion CMR test predicts an event rate (defined as cardiac death or nonfatal myocardial infarction) of 0.7% in the first and second year after a normal perfusion test and 0.8% per year over a 3-year period after the test (6). Interestingly, the likelihood for event-free survival was identical to that in SPECT studies, whereas more events occurred in the positive arm of the study, demonstrating a higher prevalence of disease in the CMR study compared to previous SPECT studies. In the acute setting, a negative perfusion CMR showed 100% sensitivity and a positive perfusion CMR showed 91% specificity to predict future adverse cardiac events (7).

**Safety.** CMR has an excellent safety profile. If the contraindications are followed, no harm from the magnetic field has been demonstrated. The major concerns are claustrophobia, occurring in approximately 2% of the patients, and side effects of the gadolinium-containing contrast agent. Whereas these agents have no effects on kidney function and only very rarely lead to (mild) allergic reactions, the induction of nephrogenic systemic fibrosis has been recently discussed. Fortunately, the use of low contrast agent doses, as routinely used for CMR perfusion imaging, has not been shown to have caused a single case of nephrogenic systemic fibrosis so far.

**Technique limitations.** CMR is a low-energy technique and, therefore, has no significant side effects as related to radiation. Conversely, however, especially in combination with high-resolution imaging (3 × 3 mm in today’s standard techniques), images are noisier and have more artefacts than do perfusion images from high-energy techniques (CT, SPECT, positron emission tomography) or other magnetic resonance images (for example, late gadolinium enhancement or cine images). Consequently, reading the images is not always straightforward and requires some experience. Fortunately, it is possible to decide on the presence and type of artifact based on the images, and thus decide early in the analysis process whether to refrain from analysis (in rare cases) or to exclude some segments. In approximately 85% of cases no significant artifacts are found.

A second potential limitation is the rapid progress of the technique, limiting standardization and confusing some (potential) users. This rapid progress is related to the urge of researchers to minimize artefacts, allow for full quantification, and come up with even higher spatial resolution imaging (for example, 1 mm × 1 mm). Even though that introduces a multitude of techniques, there are several basic techniques available that are implemented on most magnetic resonance scanners in use today and have been adequately validated in multicenter settings.
Interestingly, most limitations observed with previous perfusion techniques are less of a problem. Patients with multivessel disease can be accurately identified, since the problem of “balanced ischemia” seems to be overcome by the ability to discriminate endocardial and epicardial perfusion. Patients who have had bypass surgery or previous myocardial infarction can be readily examined. Owing to the high spatial resolution, it is possible to address complex perfusion patterns and detect peri-infarct ischemia. Clearly, for many patients, the combination of perfusion imaging with scar imaging (late gadolinium enhancement) is valuable, because the accurate visualization of a necrotic area allows for good discrimination of irreversible and reversible damage.

Future. In the future, we will see 2 major developments. First, many centers will move toward full quantification of myocardial blood flow. That will allow for not only determining the effect of therapy but also better addressing the severity, rather than only the extent, of disease. Second, the importance and presence of subendocardial ischemia and its differentiation from epicardial coronary artery disease will be better understood. The impact of these findings on clinical medicine then needs to be addressed.

Why CMR? Clearly, a well-validated, highly accurate, rapid, noninvasive technique without the use of radiation and using a small dose of a well-tolerated contrast agent is the best approach to deliver good medicine to our patients.

The higher complexity of CMR imaging in comparison with some other techniques (for example, CT or SPECT) does not allow us to use these simpler techniques at a cost to the patient (for example, applying radiation), but should rather force us to continue to learn and force the vendors to simplify magnetic resonance imaging as a whole.

Combined Coronary Angiography and Myocardial Perfusion Imaging by CT: The Future May Be Closer Than Anticipated

João A. C. Lima, MD
Richard T. George, MD

The current management of symptomatic patients with suspected coronary artery disease (CAD) frequently begins with attempts to detect coronary stenosis causing a myocardial perfusion defect by using nuclear isotopic techniques. The identification of such lesions generally leads to invasive coronary angiography for further documentation of vessel stenosis, anatomic characterization, and suitability for catheter-based intervention or surgery if clinically indicated. More recently, the advent of CT angiography suggests that the option of beginning the workup of younger patients with suspected CAD with an anatomic-based study, instead of a test designed to look at myocardial perfusion, makes a lot of sense. Indeed, the possibility of coupling anatomic and functional information in 1 single test tailored to the needs of specific patients could have important implications for the evaluation of CAD clinically.

The notion that CT could provide information on myocardial perfusion has been documented in the past by investigators using electron beam CT (8). However, the combination of a reliable coronary angiogram with stress-induced myocardial perfusion assessment had to wait until spiral CT technology progressed sufficiently to enable the acquisition of 64 slices simultaneously (9,10). Currently, the greatest limitations to CT coronary angiography are the presence of severely calcified coronary segments, stents, or other artifacts that limit luminal visualization. Patients with calcified arteries tend to be older and/or have advanced CAD. Their studies are challenging from a diagnostic viewpoint because vulnerable plaques and stenotic lesions may be hidden underneath large amounts of calcium accumulated in the outer portions of atherosclerotic plaques encompassing 1 or more segments. While progress in multidetector technology has improved our ability to study such patients, greater coverage and improved temporal resolution are unlikely to eliminate the problem, which is in large part intrinsic to the pathogenesis of atherosclerosis, namely, plaques grow outwardly first and tend to accumulate calcium as part of the healing process, therefore creating a natural shield to X-ray penetration. That is a particular limitation to the study of older persons, patients with advanced CAD, and patients who underwent coronary artery bypass graft surgery or multiple stent implantation, as well as patients with diseases such as chronic renal failure that accelerate plaque calcification.

Initial subclinical studies documenting the possibility of translating these methods to humans indicate that the combination of coronary angiograms with measurements of relative differences in myocardial blood flow during stress are feasible with current 64-slice multidetector computed tomography (MDCT) technology (9,11). Previous work using CMR to measure myocardial perfusion suggests that most of the needed information is provided by the stress images. However, differentiation between stress-induced perfusion defects and myocardial scar such as old infarcts or myocardial fibrosis secondary to previous myocardial damage or due to other disease processes hampers the use of stress studies only. Thus, baseline...
studies at rest are crucial for the full implementation of this technology. In this regard, the main obstacle for its full implementation has been the magnitude of radiation that would be needed for the acquisition of myocardial perfusion information not only during stress, but also at rest using current 64-row MDCT technology with retrospective gating.

Recent developments in MDCT technology that would allow for prospective gating during 64-row MDCT (12), or for complete myocardial imaging during 1 gantry rotation (13), have created the possibility of reducing radiation exposure enough to enable the performance of combined angiography and myocardial perfusion assessment at rest and during stress. It is feasible to perform both studies with current techniques and a total of 8 to 10 millisieverts. Moreover, if the coronary angiogram provides the complete diagnostic picture, the cardiologist could elect not to perform a perfusion study. Based on current studies of patients with suspected coronary artery disease (14), we estimate that perfusion imaging would be required in only 25% to 30% of cases, depending on the type of population being studied. Such techniques would be ideal for the assessment of the patient with chest pain and history of advanced disease, expected to have calcified coronaries or previously placed coronary stents. It is possible that the addition of perfusion information to the angiographic study would increase the test sensitivity to flow-limiting lesions and facilitate the indication for revascularization procedures even for patients without extensively calcified arteries or coronary stents, based on the combination of anatomic plus functional information.

Moreover, recent attention to patients with chest pain but no obstructive epicardial CAD (microvascular ischemia) (15) has demonstrated that, for a substantial proportion of these patients, microvascular processes can be identified by perfusion reserve measurements in association with traditional CAD risk factors such as hypercholesterolemia, hypertension, smoking, and diabetes mellitus (16). The possibility of quantifying epicardial coronary plaque burden while also assessing microvascular disease during maximal vasodilation by MDCT angiography would have profound implications for the future evaluation of symptomatic persons at risk of developing complications of CAD. For populations with a majority of Hispanic, African-American, and Asian individuals, one would expect that chest pain due to microvascular disease secondary to diabetes and hypertension may be as prevalent as chest pain caused by epicardial coronary artery obstruction. The possibility of performing a test that quickly differentiates between the 2 processes and their combination could be of great value clinically.

The advent of 320-row MDCT technology has allowed for the performance of baseline angiographic and stress perfusion studies at reasonable levels of radiation (17). Considering the fast pace of progression of MDCT technology, it is reasonable to speculate that, indeed, the future may be closer than previously anticipated.

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