EDITORIAL VIEW-POINT:
THE CHALLENGES OF MULTI-MODALITY CARDIAC IMAGING

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Invasive coronary angiography is a great method to visualize the coronary anatomy and determine the presence and severity of coronary stenosis. The assumption has been a stenosis of 50% (diameter narrowing) or greater is marker of ‘significant’ stenosis implying that it limits normal augmentation of myocardial blood flow (MBF). This threshold was used in determining the accuracy of other tests and to decide on treatment strategies. Decades later it became clear that stenosis severity is a poor marker of the physiology of coronary circulation and specifically MBF because the changes in MBF are dependent not only on the resistance in the focal stenosis but also on downstream resistance due to microvascular disease and endothelial dysfunction. These conclusions were derived from elegant studies comparing state-of-the art measurement of stenosis severity with state-of-the art measurement of MBF or pressure gradients across coronary stenoses of different severities.

The MBF is tightly regulated in normal subjects by myocardial oxygen demand (MVO-2) and often remains normal at baseline (resting MBF) despite focal stenosis due to a process of autoregulation. In response to increased demand such as exercise, the MBF increases several folds (peak, or hyperemic MBF). The ratio of the peak to resting is referred to as coronary flow reserve (CFR). In general the peak MBF and CFR are lower in the presence of coronary stenosis than in normal subjects and if the reduction is severe enough, then myocardial ischemia is produced with its clinical manifestations (chest pains or shortness of breath), ECG changes (ST depression or elevation), left ventricular (LV) wall motion abnormalities or perfusion abnormalities. This cascade of changes is the principle of using non-invasive imaging to detect coronary artery disease (CAD).

It was not too long ago that treadmill exercise testing (TET) or its counter-part, the bicycle exercise test in Europe was the only non-invasive stress modality. The TET was used to detect CAD, predict outcome and assess efficacy of new medications and interventions as for approval by the Food and Drug administration (FDA). With decades of experience, we have come to recognize its strengths and limitations, and in the process introduce many modifications, protocols, definitions and scoring systems with the said purpose of improving the precision of the test. Obviously back then the ST response was considered the single most important variable of the TET but with time we have come to recognize that though ST response is the best variable for diagnosis, the non-ST variables especially exercise time or METS (metabolic equivalent) are far more important for prognostication.
A number of non-invasive imaging modalities (echocardiography [Echo], nuclear cardiac imaging, cardiac magnetic imaging [CMR] and cardiac computed tomography [CT]) have been introduced to study the structure and function of the heart and coronary circulation at rest and during stress.

The type of stress testing has also changed and pharmacological stress testing is now accounts for almost 60% of the stress tests done with imaging in the United States. The main indication (there are few other exceptions) for pharmacological stress testing is the inability to perform adequate exercise ‘sub-maximal exercise” because the sensitivity of any test (TET alone or TET combined with imaging) with submaximal exercise is suboptimal.

The pharmacological stress tests are mainly of 2 types: inotropic agents (dobutamine is the prototype) and coronary vasodilators (dipyridamole, adenosine, regadenoson and adenosine triphosphate). In the United States regadenoson accounts for over 80% of all pharmacological stress tests performed with nuclear imaging and dobutamine for over 90% of the stress tests performed with Echo (the numbers are different elsewhere in the world).

The principles behind stress testing (with or without imaging) is to assess directly or indirectly the ability of the MBF to respond appropriately to an increase in MVO$_2$ or to a powerful stimulus of primary vasodilation. Both TET and dobutamine increase MVO$_2$ (increases in heart rate, blood pressure and contractility) and hence the increase in MBF is a consequence to that, while the vasodilators increase MBF irrespective of the change in MVO$_2$ (uncoupling of demand and MBF). Measurement of MBF in man is difficult during peak exercise but based on many studies in man and animals, the peak is less with exercise than with vasodilators but higher than that achieved with dobutamine.

The reasons why Regadenoson (Lexiscan in United States and RapidScan elsewhere) became popular in the United states are: ease of administration (it is given as a bolus over 10 seconds rather than an infusion using an infusion pump), the use of a fixed dose regardless of body weight which eliminated errors in dose calculation and it selectivity as A-2 receptor agonist with very little or no A-1 receptor activity that is responsible for AV blocks and which explains why bolus adenosine is used to treat some forms of supraventricular tachycardia (adenosine stimulates many receptors A-I, A-2a, A-2b and A-3).
Hybrid stress testing (more than one type) is fairly common. For example the use of atropine with dobutamine in patients who do not achieve adequate target heart rates and the use of handgrip exercise or walking in place in combination with dipyridamole. Regadenoson has made it possible for yet another type of hybrid stress testing, combination of TET and regadenoson in patients undergoing TET but who fail to achieve adequate exercise. Many variants of this hybrid protocol have been used with seemingly no increase in serious side effects and a decrease in the less serious side effects.

Most large university cardiology programs in the United States provide training in all aspects of “multi-modality cardiac imaging” with variable emphasis on one or the other. There are specified training guidelines to become a user (perform, interpret and report) these imaging studies. There is further specialized training for those interested in academic career such as direct imaging laboratories.

Most stress Echo studies for detection of CAD and risk assessment are done with either dobutamine or exercise. The variables of interest are worsening in LV wall motion/thickening and changes in LV volumes and ejection fraction (EF). Myocardial perfusion pattern using microbubbles is another important variable when performed.

Most of stress CMR studies are done with vasodilator stress testing as exercise testing is not feasible. The variable of interest when performed with vasodilators is the myocardial perfusion pattern (scar or ischemia). When performed with dobutamine the variables are similar to those with Echo. CMR could also provide information on coronary anatomy (CMR angiography).

Cardiac CT provides multiple variables of interest: coronary calcium score, coronary angiography (stenosis severity soft and calcified plaques, remodeling), LV function and potentially MBF.

Nuclear imaging, which is the most widely used imaging modality in the United States, could be performed with single photon emission tomography (SPECT) or with positron emission tomography (PET). Each provides information on perfusion pattern (scar or ischemia), LV function (EF, volumes and wall motion/thickening) and in the case of PET absolute measurement of MBF (regionally and globally).

The concept of multimodality imaging is still evolving and is centered on the premise that imaging should be personalized and the most appropriate test utilized to answer specific questions. The American College of cardiology, the
American Heart Association, the European Society of Cardiology, and multiple imaging organizations have outlined appropriateness criteria for each imaging modality but these guidelines presume that there is equivalent expertise in all imaging modalities in all institutions and across practices, which is unreal. The new generation of trainees who are now being trained in multimodality imaging hold the premise that something like that will happen in the future.

There is probably overuse of imaging (studies show regional variations in the use of coronary angiography and all imaging modalities across the United States and yet the mortality rates are very similar!), inappropriate use, less than acceptable quality images and less than ideal reporting of results which when coupled with the decline in mortality due to CAD in developed countries and the decline in the incidence of abnormal test results over the last decade suggests the need for a better system of test selection and patient selection. The developing countries no doubt will have their share of issues to deal with but one is helpful that the experience so far would make it easier to adopt.


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