Dobutamine Stress MRI for the Assessment of Coronary Artery Disease: Expanding Our Field of View

Ronen Rubinshtein MD

Department of Cardiovascular Medicine, Carmel Medical Center affiliated with Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

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With recent technical and clinical advances, cardiovascular magnetic resonance imaging has evolved from a promising research tool to an everyday clinical test. CMR has changed over the last decade from a modality that was used nearly exclusively for rare clinical indications such as cardiac neoplasms or arrhythmogenic right ventricular cardiomyopathy, to one that is considered a competitive first-line test to assess common indications such as coronary artery disease [1,2]. A recent expert consensus document determined that the combination of CMR stress perfusion, function, and late gadolinium enhancement allows the use of CMR as a primary form of testing for three clinical scenarios related to CAD: a) identifying patients with CAD who have resting electrocardiographic abnormalities or are unable to exercise, b) defining patients with CAD who are candidates for interventional procedures, and c) assessing left ventricular wall motion after low dose dobutamine in patients with resting akinetic LV wall segments in order to identify those whose LV systolic function will improve after coronary revascularization (viability testing) [3].

In general, stress CMR is frequently performed with one of two protocols. The more commonly used protocol is myocardial perfusion imaging, which involves intravenous administration of a vasodilator (i.e., adenosine). Stress perfusion CMR allows the evaluation of resting LV contraction as well as detection of myocardial perfusion defects (at rest and after vasodilator stress) following the administration of gadolinium-based contrast media. Delayed enhancement imaging performed several minutes after administration of contrast allows assessment of myocardial tissue for the presence of myocardial scar or edema. An alternative protocol is dobutamine-based stress CMR, involving functional assessment of the LV. Dobutamine stress CMR is performed with increasing doses of intravenous dobutamine (and atropine) to evaluate LV contraction for regional wall motion abnormalities indicative of ischemia or infarction. DSMR is performed in a similar protocol to dobutamine stress echocardiography, and the CMR pulse sequence (steady-state free precession) commonly utilized for generating cine images during DSMR does not require the administration of contrast media.

In this issue of *IMAJ*, Hamdan et al. [4] report their initial clinical experience with DSMR in Israel. The authors performed DSMR in 30 patients with suspected or known CAD using a 1.5 Tesla scanner. Reported indications were: evaluation of myocardial ischemia, preoperative assessment and viability testing. The authors employed a standard dobutamine/atropine DSMR protocol without the use of contrast and assessed the cine images for regional wall motion abnormalities. Image quality was also subjectively evaluated for the visibility of the endocardial border (which is crucial for accurate assessment of local myocardial contraction). In 28 patients, DSMR was successfully completed during an average duration of 55 minutes. In two patients, DSMR was not completed because of claustrophobia in one and inability to achieve target heart rate in the other. The authors report excellent image quality and a near perfect intra-observer agreement for wall motion contractility, thus strengthening the common notion that CMR techniques allow highly reproducible assessment of LV function. Importantly, there were no major adverse effects related to DSMR and the authors concluded that their study confirms the feasibility, safety and excellent image quality that may be achieved with DSMR for the assessment of CAD.

Hamdan and team [4] should be commended for describing, for the first time, the successful use of DSMR in Israel and for introducing a valuable diagnostic tool for local non-invasive cardiac imagers. Their study was not intended to address all important questions related to DSMR in Israel such as its diagnostic accuracy for detection of obstructive CAD, given the small sample size and the fact that not all patients underwent subsequent coronary angiography (the reference standard). In addition, an objective assessment of image quality parameters may have allowed a comparison of the image quality with other reported CMR studies. However, the study convincingly reports the feasibility and safety of DSMR in Israel and could

CMR = cardiovascular magnetic resonance imaging
CAD = coronary artery disease
LV = left ventricular

DSMR = dobutamine stress CMR

therefore lead to a broader use of this technique.

Careful review of published literature shows that DSMR safety and efficacy have been assessed extensively. DSMR exhibits major complications (such as the development of sustained ventricular tachycardia) in less than 0.1% of subjects, findings that are similar to those observed with dobutamine stress echocardiography [5]. Research has also shown that DSMR is highly accurate in detecting ischemia, related in part to its excellent LV endocardial visualization during dobutamine/atropine stress protocols [6]. With regard to diagnostic accuracy, meta-analysis of stress CMR studies demonstrated a sensitivity of 83% and specificity of 86% for the demonstration of obstructive CAD on a per-patient level [7], and CMR tagging may even further improve the accuracy of DSMR in detecting ischemia [8]. Additionally, low dose dobutamine CMR has proven useful in identifying contractile reserve, indicative of the potential for recovering systolic function after coronary revascularization [9].

Prognostic data are also available for both vasodilator stress perfusion CMR and DSMR. Three year event-free survival has been reported at 99.2% for patients with normal stress perfusion CMR or DSMR and 83.5% for those with abnormal stress perfusion CMR or DSMR [10].

In summary, DSMR seems to be a useful tool for identifying inducible myocardial ischemia and identifying contractile reserve of LV wall motion after coronary revascularization. DSMR may be especially useful where other cardiac imaging modalities are limited or contraindicated. The results of the study by Hamdan and co-authors [4] are important, highlighting the applicability of the technique to the local setting, which should encourage clinicians to use this modality more frequently. A shorter scanning protocol (< 30 minutes) may allow a broader use of stress CMR in Israel given the limited number of available scanners and skilled personnel. Their study should also induce local professional societies (and payers) to develop appropriate-use criteria to improve patient selection for CMR.

Address for correspondence:
Dr. R. Rubinshtein
Dept. of Cardiovascular Medicine, Carmel Medical Center, Haifa 34362, Israel
Phone: (972-4) 825-0288
Fax: (972-4) 825-0972
email: ronenrub@clalit.org.il

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Capsule

Randomized dose-finding clinical trial of oncolytic immunotherapeutic vaccinia JX-594 in liver cancer

Oncolytic viruses and active immunotherapeutics have complementary mechanisms of action (MOA) that are both self-amplifying in tumors, yet the impact of dose on subject outcome is unclear. JX-594 (Pexa-Vec) is an oncolytic and immunotherapeutic vaccinia virus. To determine the optimal JX-594 dose in subjects with advanced hepatocellular carcinoma (HCC), Heo et al. conducted a randomized phase 2 dose-finding trial (n=30). Radiologists infused low or high dose JX-594 into liver tumors (days 1, 15 and 29); infusions resulted in acute detectable intravascular JX-594 genomes. Objective intrahepatic Modified Response Evaluation Criteria in Solid Tumors (mRECIST) (15%) and Choi (62%) response rates and intrahepatic disease control (50%) were equivalent in injected and distant non-injected tumors at both doses. JX-594 replication and granulocyte-macrophage colony-stimulating factor (GM-CSF) expression preceded the induction of anticancer immunity. In contrast to tumor response rate and immune endpoints, subject survival duration was significantly related to dose (median survival of 14.1 months compared to 6.7 months on the high and low dose, respectively; hazard ratio 0.39; $P = 0.020$). JX-594 demonstrated oncolytic and immunotherapy MOA, tumor responses and dose-related survival in individuals with HCC.

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