Editorial

Does Late Gadolinium Enhancement Predict Cardiac Events in Patients With Ischemic Cardiomyopathy?

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Despite improved clinical care and heightened public awareness, myocardial infarction (MI) and sudden cardiac death remain the leading causes of death in the United States. For this reason, clinical, laboratory, and electrocardiographic markers to identify those at risk for future cardiac events have been developed. In addition, both invasive (contrast angiography) and noninvasive (transthoracic echocardiography, radionuclide scintigraphy, magnetic resonance, and computer tomography) imaging markers have been identified that further supplement the clinical markers to more accurately define cardiac risk. For the most part, these imaging markers rely on rest or stress measures of left ventricular (LV) ejection fraction, regional wall motion, myocardial perfusion, or the extent of coronary atherosclerosis. With the exception of coronary artery calcification scoring generated from computer tomography image datasets, there have been few new imaging markers introduced during the past 15 years that add incremental benefit to our ability to identify cardiac risk.

Late gadolinium enhancement (LGE) cardiac imaging was introduced by Saeed et al in 1989, to identify infarcted myocardial tissue during cardiovascular magnetic resonance (CMR). This technique incorporates the administration of relatively inert extracellular gadolinium contrast during gradient-echo inversion recovery imaging. On image acquisition, areas of noninfarcted tissue appear dark, and infarcted or fibrotic tissue appears bright because of reduced clearance and increased volume of distribution of the gadolinium. This fundamental aspect of delayed enhancement imaging has led to the recent expression, “bright is dead.”

Combining the ability to characterize myocardial tissue with the heightened spatial resolution of CMR (voxel sizes are commonly acquired in the range of 1.5×1.5×6 mm), one can appreciate clear, crisp borders of infarct zones that are nearly identical to those observed histopathologically. In humans, the technique is reproducible, exhibits low intraobserver and interobserver variability, and has the capability to appreciate small infarcts of ≤2 g of myocardial tissue. The implementation of the technique in humans has allowed for the noninvasive visualization and differentiation of subendocardial versus transmural infarcts without ionizing radiation or acoustic window limitations.

In the setting of resting regional myocardial dysfunction caused by ischemic cardiomyopathy, the amount of myocardial tissue exhibiting LGE is inversely proportional to the likelihood of recovery of systolic thickening that occurs after coronary artery revascularization. In this setting, LGE identifies infarcted or fibrotic tissue, whereas its absence indicates “viable” myocardium that exhibits high potential to recover myocardial function after restoration of blood flow. In patients with nonischemic cardiomyopathy, the location of LGE within the midwall of the left ventricle has been associated with an infectious or inflammatory pathology of the LV dysfunction. In short, the presence, amount, and location of LGE are helpful for diagnosing the cause of LV dysfunction and determining therapy to restore LV contractility.

To date, however, few investigators have researched the efficacy of LGE for predicting cardiac events. In this issue of Circulation, Kwong et al implemented LGE in a consecutive series of 195 patients, age 59±13 years, without known prior MI but with a clinical suspicion of an ischemic cardiomyopathy. After CMR imaging, participants were divided into one of 2 groups, according to the presence or absence of LGE, and then were followed up for an average of 16 months to determine the incidence of cardiac death, new acute MI, unstable angina or heart failure requiring hospitalization, or ventricular arrhythmias prompting an appropriate discharge from an internal cardiac defibrillator (ICD). Thirty-one patients (16%) had one of these major adverse cardiac events (MACE), including 17 cardiac deaths (7 nonsudden and 10 outpatient sudden cardiac deaths), 6 with unstable angina, 5 exacerbations of heart failure, and 3 episodes of sustained ventricular tachycardia necessitating an ICD discharge. The presence of LGE was associated with a higher incidence of MACE and was the best overall multivariable predictor of MACE, according to the Cox proportional-hazards regression model. As shown by Kwong et al, a very small amount of LGE (<2% of the mean LV mass for the individual participant) was associated with a >7-fold increase in MACE. The investigators note that potentially 13 (10 sudden deaths and 3 ICD discharges) of the 31 events may have been related to life-threatening arrhythmias. This observation is intriguing, given that LGE identifies fibrosis, and ventricular dysrhythmia can emanate from areas of slow and/or discontinuous conduction in border zones of infarcts.
where islets of live myocardial tissue are surrounded by fibrosis and scar.\textsuperscript{30,31} Given the high expense (Medicare reimbursed $1.2 billion for ICD procedures in 2002\textsuperscript{22}) associated with therapy that involves implantation of an ICD, a new noninvasive marker for identifying those at risk of sudden cardiac death caused by ventricular dysrhythmia would have high clinical utility.

Although the results of the study by Kwong et al\textsuperscript{29} demonstrate an association between LGE and future cardiac events, further data appear warranted to determine whether LGE represents an independent predictor of adverse cardiac outcome. In this study population, it is important to recognize that participants with LGE exhibited multiple established risk factors for cardiac events that may have confounded the results. As shown in Kwong and colleagues’ Table 1, participants with LGE exhibited a lower LV ejection fraction (an average of 41\% versus 60\% in those without LGE), more risk factors for coronary arteriosclerosis, a greater percentage of coronary arteriosclerosis, and a higher number of electrocardiographic findings associated with adverse cardiac outcomes.

To account for this potential confounding within the data, the investigators appropriately implemented 2 different multivariable strategies to adjust for the baseline discrepancies noted in the study population: (1) “a model that describes incremental contributions of variables,” as shown in their Table 3, and (2) a “best” predictive model, as shown in their Table 4.\textsuperscript{29} Because of the relatively small number of events and sample size, these strategies were the best efforts available to address potential confounding. The data in Table 3 demonstrate that adding LGE to known clinical predictors with one additional important variable, such as LV ejection fraction, is more predictive of cardiac events than the model with the clinical predictors and important variable alone. Unfortunately, there are many known risk factors for a cardiac event in many of the subjects. It would be more convincing if they had a larger sample size to demonstrate the effect of fitting a comprehensive model with all significant variables (identified in Kwong and colleagues’ Tables 1 and 2)\textsuperscript{29} with and without LGE. Clinically, this latter strategy would seem preferable because patients with ischemic cardiomyopathy often exhibit multiple risk factors for a cardiac event.

Kwong and colleagues’ Table 4 confirms that when considering all variables, LGE would be the first to enter a predictive model, and that once it is included, few other variables would be included or offer any additional predictive value.\textsuperscript{29} Although this approach confirms that LGE is a strong predictor of cardiac events, it does not address the question that if we fit a comprehensive model that included all previously known risk factors for cardiac events, would we still need to include the new measure of LGE? A more informative analysis would have been to fit the best predictive model without LGE being considered and then to test whether LGE still added additional predictive power to that model. Essentially, this would be a combination of the methods used to supply the data provided in Tables 3 and 4.\textsuperscript{29}

Could this latter strategy be implemented with the dataset of Kwong et al?\textsuperscript{29} The answer to this question is probably not, because of the limited number of events incurred by the study population (cardiac mortality, n=17; or MACE, n=31). In general, for each risk factor included in a multivariable model (such as a Cox proportional hazards regression model), several primary outcome events must be incurred within the study population during longitudinal follow-up; otherwise the estimation of the parameters for the model will be unstable. On the basis of the data in Kwong and colleagues’ Tables 1 and 2,\textsuperscript{29} there are as many as 10 known risk factors that should be considered for inclusion in a predictive model for MACE or cardiac mortality. To avoid instability in a multivariate analysis, at least 60 events (rather than the 31 that were observed) would need to occur during longitudinal follow-up to avoid instability in the model. Along these lines of reasoning, it will be interesting to learn after the study population experiences a greater number of cardiac events whether the conclusions of Kwong et al are sustained after controlling for more prognostic factors.

What considerations should be given to future studies to determine if LGE is an independent predictor of future cardiac events? First, larger numbers of patients with higher numbers of cardiac events must be studied. In particular, one would like to be able to identify a large group of patients with and without MACE who actually had similar risk factor profiles (for traditional risk factors of cardiac events, such as LV ejection fraction) and then examine whether the presence of LGE identified future MI, cardiac death, or malignant arrhythmias. Second, rather than treat LGE as a dichotomous variable (presence versus absence), it would be useful to understand whether the amount or location of LGE is more or less predictive of a cardiac event. This strategy would allow for LGE to be assessed as a continuous variable. It will be interesting to know whether the inverse relation between the amount of LGE and recovery of thickening after coronary artery revascularization also holds true for prediction of cardiac events. Finally, it will be important to determine the utility of LGE in patients with various causes for their underlying cardiomyopathy. For example, does LGE prognosticate cardiac events in patients with a nonischemic cardiomyopathy (toxin, infection, or inflammation) to the same degree it may with an ischemic association?

In summary, Kwong et al\textsuperscript{29} are to be commended for accumulating and reporting this prognostic data on LGE. The results are intriguing, given the fact that LGE may serve as a new prognostic indicator, based on its ability to appreciate myocardial injury and fibrosis. Although the results from the study by Kwong et al indicate an association between LGE and cardiac events, further studies with larger patient numbers and higher event rates are required to determine if LGE represents an independent predictor of cardiac events when a patient possesses multiple known risk factors for an adverse cardiac outcome. In addition, further investigation is needed to determine whether the amount or location of LGE independently predicts cardiac events or whether LGE forecasts cardiac events in patients without an ischemic cardiomyopathy.

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