Late Gadolinium Enhancement by Cardiac Magnetic Resonance Imaging and Major Adverse Coronary Events

Kolten Paryzek

Chase Beal

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Abstract

Background: Coronary artery disease is the most common type of heart disease. CAD encompasses atherosclerosis and arteriosclerosis and is the leading cause of death in the United States in both men and women. This disease process involves the blood vessels responsible for supplying blood to the heart. Arteriosclerosis is described as a hardening of the vessels, while atherosclerosis is the obstruction of vessels due to genetics and dietary/lifestyle activities. In the long-term, these abnormalities can lead to myocardial infarction (MI), valvular heart disease, chest pain or angina, and heart failure.

Standard practice of care currently involves the use electrocardiogram (ECG), computed tomography (CT), and echocardiogram in order to monitor cardiac function. A new emerging imaging study, cardiac magnetic resonance with late gadolinium enhancement, has shown to be a promising prognostic tool in evaluating patient's risks for major adverse coronary events (MACE).

CMR is a medical imaging technology for non-invasive assessment for the function and structure of the heart. Gadolinium is a contrast agent that can be injected during the CMR study that localizes in cardiac cicatrix tissue. If the imaging study has a positive result, it may lend evidence that cardiac function is below optimal and may put patient at risk for MACE in the future.

Methods: An exhaustive search of available medical literature was performed using the following databases: MEDLINE-OVID, MEDLINE-Pubmed, and CINAHL-EBSCO Host. Articles were discovered using the following terms: MRI, Coronary heart disease, gadolinium, LGE, and cicatrix. Relevant articles were assessed for quality using GRADE.

Results: Three studies met the inclusion criteria and were included in this systematic review. All three of these cohort studies demonstrated that the presence of scar tissue, identified by late gadolinium enhancement (LGE), had a positive predictive value of major adverse cardiac events (MACE) in patients with symptoms or signs suspicious of coronary artery disease (CAD). Studies demonstrated hazard ratios for MACE in LGE positive patients ranging from 4.69 to 11.48.

Conclusion: The use of late gadolinium enhancement as an adjunct to cardiac magnetic resonance (CMR) testing has shown to be a valuable asset in predicting major adverse coronary events such as myocardial infarction and cardiac death. These events were followed for an accumulative median of 19 months, spanning from 6 months to 4.7 years. From the high-quality evidence gathered, LGE was a strong predictor of MACE and may have an invaluable future in stratifying risk among patient populations with clinical CAD.

Keywords: MRI, coronary heart disease, gadolinium, and cicatrix.

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Late Gadolinium Enhancement by Cardiac Magnetic Resonance Imaging and Major Adverse Coronary Events

Kolten Paryzek and Chase Beal

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies Pacific University Hillsboro, OR

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Faculty Advisor: Saje Davis-Risen and Elizabeth Crawford

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[Redacted for privacy]
Abstract

Background: Coronary artery disease is the most common type of heart disease. CAD encompasses atherosclerosis and arteriosclerosis and is the leading cause of death in the United States in both men and women. This disease process involves the blood vessels responsible for supplying blood to the heart. Arteriosclerosis is described as a hardening of the vessels, while atherosclerosis is the obstruction of vessels due to genetics and dietary/lifestyle activities. In the long-term, these abnormalities can lead to myocardial infarction (MI), valvular heart disease, chest pain or angina, and heart failure.

Standard practice of care currently involves the use electrocardiogram (ECG), computed tomography (CT), and echocardiogram in order to monitor cardiac function. A new emerging imaging study, cardiac magnetic resonance with late gadolinium enhancement, has shown to be a promising prognostic tool in evaluating patient’s risks for major adverse coronary events (MACE).

CMR is a medical imaging technology for non-invasive assessment for the function and structure of the heart. Gadolinium is a contrast agent that can be injected during the CMR study that localizes in cardiac cicatrix tissue. If the imaging study has a positive result, it may lend evidence that cardiac function is below optimal and may put patient at risk for MACE in the future.

Methods: An exhaustive search of available medical literature was performed using the following databases: MEDLINE-OVID, MEDLINE-Pubmed, and CINAHL-EBSCO Host. Articles were discovered using the following terms: MRI, Coronary heart disease, gadolinium, LGE, and cicatrix. Relevant articles were assessed for quality using GRADE.

Results: Three studies met the inclusion criteria and were included in this systematic review. All three of these cohort studies demonstrated that the presence of scar tissue, identified by late gadolinium enhancement (LGE), had a positive predictive value of major adverse cardiac events (MACE) in patients with symptoms or signs suspicious of coronary artery disease (CAD). Studies demonstrated hazard ratios...
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**Conclusion:** The use of late gadolinium enhancement as an adjunct to cardiac magnetic resonance (CMR) testing has shown to be a valuable asset in predicting major adverse coronary events such as myocardial infarction and cardiac death. These events were followed for an accumulative median of 19 months, spanning from 6 months to 4.7 years. From the high-quality evidence gathered, LGE was a strong predictor of MACE and may have an invaluable future in stratifying risk among patient populations with clinical CAD.

**Keywords:** MRI, coronary heart disease, gadolinium, and cicatrix.
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Table I: Quality Assessment of Reviewed Articles

List of Abbreviations

LGE Late Gadolinium Enhancement
CAD Coronary Artery Disease
MACE Major Adverse Cardiac Events
CMR Cardiac magnetic Resonance
MI Myocardial Infarction
CT Computed Tomography
ECG Electrocardiogram
Late Gadolinium Enhancement by Cardiac Magnetic Resonance Imaging and Major Adverse Coronary Events

BACKGROUND

Coronary artery disease (CAD) is the most common type of heart disease. CAD encompasses atherosclerosis and arteriosclerosis and is the leading cause of death in the United States in both men and women.\(^1\) Arteriosclerosis is described as a hardening of the vessels, while atherosclerosis is the obstruction of vessels due to genetics and dietary or lifestyle activities. In the long-term, these abnormalities can lead to myocardial infarction (MI), valvular heart disease, chest pain or angina, and heart failure.

Standard practice of care currently involves the use electrocardiogram (ECG), computed tomography (CT), and echocardiogram in order to monitor cardiac function. A new emerging imaging study, cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE), has shown to be a promising prognostic tool in evaluating patient’s risks for major adverse coronary events (MACE).

The original purpose of LGE was to image cardiac scarring. It was soon discovered that it could be used to diagnose specific cardiomyopathies based on the pattern of gadolinium absorption in tissue as well as a reliable predictor of future cardiomyopathies and MACE. CMR is a medical imaging technology for non-invasive assessment for the function and structure of the heart. Gadolinium is a contrast agent that can be injected during the CMR study that localizes in cardiac cicatrix tissue.\(^2\) If the imaging study has a positive result, it may give evidence that cardiac function is below optimal which puts the patient at risk for MACE in the future.
METHODS

An exhaustive literature search of available medical literature was performed using the following databases: MEDLINE-OVID, MEDLINE-Pubmed, and CINAHL-EBSCO Host. Articles were discovered using the following terms: MRI, coronary heart disease, gadolinium, LGE, and cicatrix. The search was narrowed to use English language articles and human trials only. Bibliographies of relevant articles were searched for additional sources of information. Relevant articles were assessed for quality using Grade of Recommendations, Assessment, Development, and Education (GRADE).

RESULTS

An initial search revealed a total of 5 studies. After inclusion criteria was applied, 3 studies\textsuperscript{3-5} were included in this systematic review. All 3 of these cohort studies demonstrated that the presence of scar tissue, identified by late gadolinium enhancement (LGE), had a positive predictive value of major adverse cardiac events (MACE) in patients with symptoms or signs suspicious of coronary artery disease (CAD).

Krittayaphong et al

The objective of this cohort study\textsuperscript{3} was to determine the prognosis of patients who displayed normal ventricular wall motion with clinical evidence of CAD and the possibility of an unrecognized past myocardial infarction. There were 1713 patients who were initially gathered to be included in this study. Patients were included in this study if they had known or suspected CAD, were more than 30 years old, and CMR showed normal wall function.\textsuperscript{5}

Patients were excluded if they had contraindications for CMR such as pacemakers
or internal defibrillators, histories of any myocardial infarction, poor quality images of myocardial function, inability to complete the CMR exam as requested, histories of revascularization such as angiography, dilated cardiomyopathies, hypertrophic cardiomyopathy, myocarditis, cardiac amyloidosis, clinically unstable conditions, and if follow-up had failed to be completed. As a result, 565 patients were excluded from the study, leaving 1148 patients with normal left ventricular wall motion to be included. Average age was 64.6 +/- 11.3 years and had an average follow-up of 955 +/- 542 days.3

LGE was positive in 104 patients (9%). For patients who had a positive LGE study, the statistics for hard cardiac events (ie, death or MI) and MACE had hazard ratios of 8.59 (3.23-24.37) and 4.69 (2.28-9.67), respectively. From this data it was found that LGE positive patients had an increased risk of cardiovascular events compared to patients without a positive study.3

It was determined that LGE was the best prognostic tool in determining hard cardiac events and MACE. As demonstrated by the following subgroup analysis. Out of those 104 patients with positive LGE the major following factors: male gender (63.5%), hypercholesterolemia (74%), and hypertension (73.1%). During the allotted time, 18 patients had hard cardiac events (ie, death or MI). The subgroups of these 18 patients of the LGE positive group are as follows: male gender (HR 1.42, CI 0.56-23.57, P=0.655), hypercholesterolemia (HR 0.95, CI 0.37-2.44, P=0.909), and hypertension (HR 0.73, CI 0.29-1.86, P=0.514). Also during the allotted time, 54 patients experienced MACE. The subgroups of these 54 patients in the LGE positive group are as follows: male gender (HR 1.13, CI 0.66-1.93, P=0.655), hypercholesterolemia (HR 1.22, CI 0.69-2.15, P=0.487), and hypertension (HR 1.10, CI 0.63-1.93, P=0.73). These subgroup hazard
ratios demonstrate that LGE can identify patients at risk for MACE independently of other common risk factors.\textsuperscript{3}

The limitations of this study, as described by the authors, are that left ventricular hypertrophy and aortic stenosis and were not excluded and may have a relationship with LGE. Secondly, abnormal wall motion was assessed visually and not with a quantitative tool, lending itself to subjective bias. Lastly, the study did not consider the possibility of outside influences having an effect on wall motion abnormality and perfusion abnormalities, which could change the clinical outcome.\textsuperscript{3}

\textbf{Kwong et al}

The purpose of this study\textsuperscript{4} was to evaluate the prognostic value of LGE in CMR studies due to the fact that 25% of myocardial infarctions go unrecognized by ECG and lack any wall motion abnormalities when using CMR. Alternative cardiac function imaging studies are needed to more accurately stratify long-term risk in vulnerable populations. The initial study population was 221 patients, who were included due to possessing signs and symptoms consistent with CAD and had been evaluated by CMR imaging.\textsuperscript{4}

The exclusion criteria included having a history of myocardial infarctions, suspected or confirmed myocarditis or cardiomyopathies (including amyloidosis, cardiac hemochromatosis or sarcoidosis), any pericardial diseases, unstable angina, class IV heart failure, hemodynamic instability, claustrophobia, and metallic hazards. Patients that lacked coronary stenosis 2 weeks before CMR were also excluded. As a result of the exclusion criteria, 195 patients remained in the study. Follow-up with patients included
phone interviews, contacting the patient’s physician, or accessing medical records. Length of follow-up ranged from 6 to 42 months.\(^4\)

By the conclusion of the study, 31 (16%) patients had experienced MACE, including 17 cardiac deaths, 6 unstable angina events, 5 exacerbations of heart failure, and 3 ventricular tachycardia that required the firing of internal cardiac defibrillators. Even though other cardiac functioning tests demonstrated a connection with MACE, LGE had the most significant association with MACE and long-term cardiac mortality. The hard points for this association are as follows: unadjusted HR of 8.29 with a P-value of \(<0.0001\), and adjusted HR of 10.9 with a P-value of \(<0.001\).\(^4\)

Limitations of this study, as described by the authors, included possible clinician bias due to the patient population having to be referred to the study. This restricts the ability to immediately apply to the general population for unrecognized myocardial infarctions. Secondly, physicians evaluated coronary stenosis utilizing coronary angiography imaging at their own discretion, resulting in not every patient having the imaging study done and making it impossible to recognize if prognostic significance could be maintained.\(^4\)

**Steel et al**

Subendocardial MI can often go unrecognized by CMR. This study\(^5\) suggests that LGE is the most sensitive method for recognizing this type of MI and risk stratification of patients with known or suspected CAD. There were 264 patients who were initially included in the study. Inclusion criteria included patients who were referred to CMR by clinicians for signs and symptoms related to chest pain or stable angina.\(^5\)

Patients were excluded from the study if there was a history of acute chest pain
associated with unstable angina, heart failure, clinically unstable, contraindications for vasodilators, and metallic hazards that make them unfit for magnetic imaging. After exclusion criteria were applied, 10 patients were dropped from the study due to technical problems, leaving 254 patients to be included. Follow-up time ranged from 8 months to 4.7 years. Follow-up was completed via telephone call, mailed questionnaire, medical chart review, or contact with the patient’s physician. There were 49 cardiovascular events within the given time frame, which included 12 cardiac deaths, 16 myocardial infarctions, 19 hospitalizations due to unstable angina, and 2 cases of percutaneous intervention.5

Based on data obtained from follow-up, it was determined that 156 patients, without a history of MI, had positive LGE and resulted in an 11-fold increase in risk for cardiac death or MI. The statistics are as follows: HR 11.48 with a P-value of 0.001.

Limitations of this study, as described by the authors, included possible clinician bias due to the patient population having to be referred to the study. Secondly, although this study proved that LGE had a significant prognostic factor in established CAD patients, further studies are needed to see its applicability to patients with a lower CAD prevalence. Lastly, CMR with LGE was not directly compared to other cardiac imaging studies such as stress nuclear myocardial perfusion imaging or computed tomography angiography and therefore the efficacy in relation to other imaging studies cannot be quantified.5

**DISCUSSION**

Using late gadolinium enhancement with cardiac magnetic resonance imaging has been shown to be a valuable prognostic tool in understanding the risks that face particular patient populations who exhibit clinical signs and symptoms of heart disease. These 3
cohort studies\textsuperscript{3-5} displayed evidence that supported this theory. As stated before, coronary heart disease encompasses 2 disease processes called atherosclerosis and arteriosclerosis. Arteriosclerosis is the gradual stiffening and narrowing of blood vessels that are brought on by lifestyle habits such as smoking and family genetics. Over an extended period of time, dietary and lifestyle habits such as smoking and lack of exercise contribute to the formation of fatty cholesterol that obstructs coronary vessels that results in atherosclerosis, which is type of arteriosclerosis.

These processes open the door for poor blood perfusion to the heart and set a favorable environment for a heart attack or heart failure. In patients who possess such risk factors, it’s important to be able to categorize their unique risk of suffering any cardiovascular events so that appropriate measures can be implemented to avoid such occurrences. LGE has been proven to be even more resourceful that current diagnostic studies and tests at assessing patients risk and if put into effect, can change the face of cardiology and primary care.\textsuperscript{4}

Although the evidence from each one of the studies was compelling in it’s own right, there are several limitations that need to be taken into consideration. A limitation that was stated in all 3 articles\textsuperscript{3-5} included the fact that the study population was generated through physician referrals. Also, the management of the patients were under direct supervision of their physicians, meaning that important treatment decisions regarding medications, revascularizations, and catheterizations were left to the discretion of the provider and is unclear how the LGE study may have played a role in the decision making process. Due to the this limitation, these results may only be applicable to the patient population whom the physicians felt had more clinically significant cardiac
disease processes. Therefore, the applicability of the studies to the general public is still unknown and must be further studied. In one study, the use of LGE in CMR was tested independently from other cardiac functioning tests such as stress myocardial perfusion imaging and computed tomography. Therefore, the efficacy cannot be directly compared to that of the aforementioned imaging modalities in terms of prognostic value. These limitations could be absolved by additional studies with different patient populations.

CONCLUSION

The use of late gadolinium enhancement (LGE) as an adjunct to computed magnetic resonance (CMR) testing has shown to be a valuable asset in predicting major adverse coronary events such as myocardial infarction and cardiac death. These events were followed for an accumulative median of 19 months, spanning from 6 months to 4.7 years. From the high-quality evidence gathered, LGE was a strong predictor of MACE with HRs ranging from 4.69 to 11.48 and may have an invaluable future in stratifying risk among patient populations with clinical CAD.

As a clinician, LGE imaging could be implemented in patients to look at the extent of myocardial infarctions, evaluate cardiac wall motion abnormalities, and discover certain scar or fibrotic patterns with cardiomyopathies that may lead to MACE in the future. All diagnostic cardiac imaging pathways, including LGE, are considered to be cost-effective when being compared to no testing at all. However, more research must be completed to further assess the cost-effectiveness of LGE against more standard diagnostic modalities.
Reference


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\(^a\) HR of 8.59 for MACE and Hard Events (death/MI)
\(^b\) HR of 8.29 for MACE (unadjusted) and HR of 10.9 (adjusted) for cardiac mortality
\(^c\) HR of 11.48 for death/MI