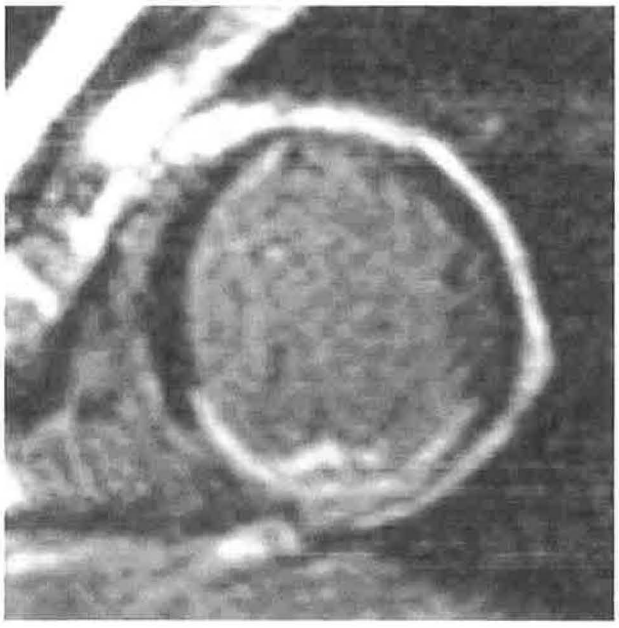
# Cardiac Magnetic Resonance: Is a Picture Worth a Thousand Words?



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Dr. Reimold is a non-invasive cardiologist with a focus in Cardiac Imaging, including echocardiography and cardiac magnetic resonance imaging. She is the Medical Director of the UT Clinical Heart Center.

Dr. Reimold will be discussing off-label uses of gadolinium in this presentation. There are no conflicts of interest.

Cardiac magnetic resonance (CMR) is a rapidly emerging cardiac imaging technique. While there has been substantial interest in the application of cardiac MR to identify coronary arteries and detect coronary artery disease, recent attention has focused on the use of CMR for the evaluation of myocardial diseases. Today's discussion will describe the basic functional study used to assess left ventricular and right ventricular function, the technique of delayed enhancement CMR as well as several applications of delayed enhancement. The focus of these applications will be on patients with left ventricular dysfunction and will include the use of delayed enhancement for determining the etiology of heart failure, myocardial viability in patients with coronary artery disease, efficacy of beta blockers in heart failure, and the prognosis in patients with hypertrophic cardiomyopathy. Lastly, I will describe the research directions in cardiac MR here at UT Southwestern.

**Functional Study**

The basic functional study consists of two chamber, four chamber, long axis, and short axis views of the left ventricle. Scout images are obtained to allow identification of standard cardiac landmarks. Functional cine images are acquired using a single breath hold technique. Single breath hold techniques are important because it essentially eliminates the movement of the heart within the thoracic cavity with respiration. The duration of the breath hold varies and is inversely related to heart rate. New imaging sequences known as True-FISP and BFFE improve structural resolution and definition of the blood pool/myocardial border with moving images.

Quantitation of left and right ventricular systolic function is performed using MRI using the method of discs. Cine two dimensional images are obtained through every 10 mm of the left ventricle. Endocardial and epicardial borders are traced on end diastolic and end systolic frames. Using these frames, quantitation of left and right ventricular volumes and left ventricular mass is possible for each disc. Volumes and mass of each disc are added together to determine overall left ventricular mass, left and right ventricular volumes.

This technique has been performed in a large number of normal individuals to establish the normal range. The normal ranges for left ventricular end diastolic volume, end systolic volume, stroke volume, ejection fraction and LV mass are shown in Figure 1. End diastolic volume and end systolic volume are greater for men as opposed to women. The gender difference in volumes can largely be eliminated by correction of these volumes for body surface area. The normal ejection fraction by CMR is 67% and generally runs in most studies approximately 5% higher than measurements of ejection fraction by either radio ventriculography or echocardiography (1,2). Measurement of mass and chamber volumes is extremely reproducible by CMR. This increased ability to make reproducible and accurate measurements has been utilized in clinical trials because the ability to statistically detect small differences in LV mass or volume is now possible decreasing the number of patients needing to be enrolled to demonstrate a statistically

significant change. Whether such relatively small changes in these measured variables are clinically relevant is yet to be determined (3).

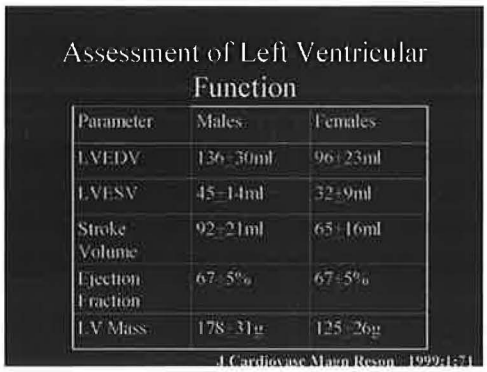


Figure 1. Table of left ventricular volumes, ejection fraction, and mass according to sex (1).

**Contrast CMR**

Contrast agents are used in most imaging fields. In angiography, contrast agents are used to delineate the lumen of a vessel. In echocardiography, contrast is used to help identify the border between the blood cavity and the endocardium. Gadolinium based agents have been used as contrast agents in MRI since 1984. While it is an approved contrast agent for use in central nervous system imaging, cardiac applications represent an off-label use of the medication. It is used not only for angiography in the vasculature, but is used for delineation of myocardial abnormalities. When Gadolinium is administered to the heart, it reaches the heart in proportion to blood flow. In normal myocardium with normal perfusion, there is a rapid wash-in and wash-out. In damaged myocardium, however, with intact perfusion there is a rapid wash-in and a delayed wash-out. In areas without adequate perfusion and abnormal myocardium there is slow wash-in and markedly delayed wash-out in these areas.

Performing contrast CMR is a simple procedure (4,5). An intravenous line is placed and a bolus injection of Gadolinium is administered. The operator then waits 5-10 minutes and T1 weighted images are obtained. Delayed contrast CMR images are obtained with special sequences known as inversion recovery sequences. The operator alters the inversion recovery time to separate out normal myocardium from abnormal myocardium. At the optimal inversion recovery time, normal myocardium is nulled and will appear black. The presence of Gadolinium alters the T1 recovery time of abnormal myocardium allowing for increased differences between the appearance of normal and abnormal myocardium.

In a more understandable schematic, normal myocardium is seen on the left (Figure 2). There are intact cell membranes and the interstitium around them with normal distribution of ions. Gadolinium has been administered; it does not go into the cell membranes because they are intact and it is then eliminated from the interstitium. In

the presence of an acute infarction there is disruption of the cell membranes and increased diffusing capacity (center image). In scar formation there is elimination of most if not all of the myocardial cell membranes leaving an extensive collagen matrix. Gadolinium may be distributed to that area and leave the area very slowly. These areas will appear white in contrast to the normal myocardium on contrast enhanced scans. Gadolinium has been available for imaging for nearly 20 years, yet it is only in the last 3-4 years that it has gained hold in terms of having an important role in cardiac imaging. This is largely due to improvement in sequences and capabilities of contemporary magnetic scanners. Several phrases are used to describe delayed enhancement scanning including contrast enhanced, hyperenhanced, and delayed enhancement. Throughout the rest of the discussion ceCMR will be used to denote this entity.

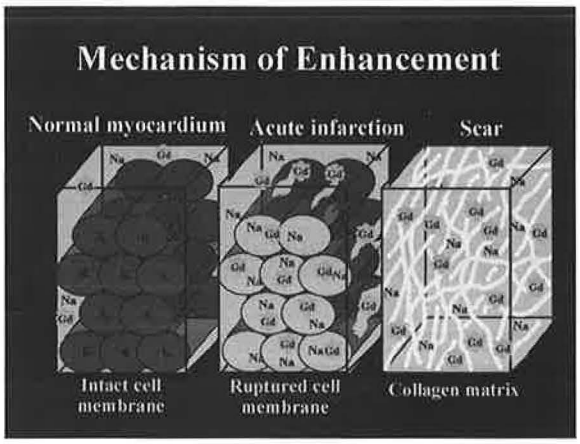


Figure 2. Depiction of myocardial cells, interstitium and gadolinium

**Pathologic Correlation and Reproducibility of Delayed Enhancement CMR**

There is an excellent correlation between Gadolinium ceCMR and pathologic findings. There is a close correlation between the size of an acute myocardial infarction in the animal model and the delayed enhancement seen by ceCMR prior to sacrifice (6). This is true not only in this acute setting but in the chronic infarction setting (Figure 3). Gadolinium enhancement correlates with the degree of increase in collagen matrix and scar formation. Excellent correlation between infarct size and area of delayed enhancement is seen in dog models of infarction.

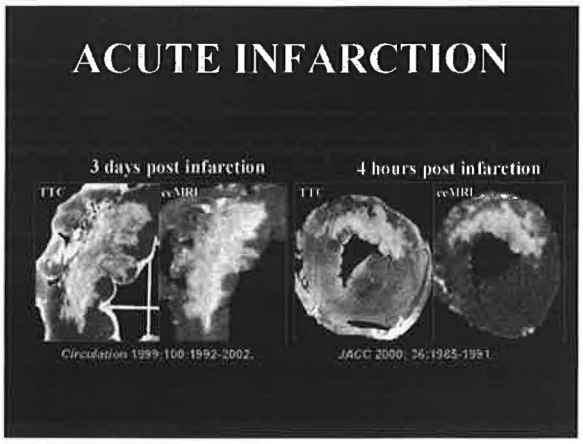


Figure 3. Close pathologic correlation with ceCMR in an animal model of acute infarction is shown.

In order to feel confident that we should use this technique widely it is important to know that it is not only reproducible but comparable to other available imaging methods. CMR was compared to nuclear Technetium Sestamibi images for comparison of infarct size (7). On a single morning patients received 2 nuclear and 2 CMR studies. The ceCMR studies were performed 10-30 minutes after initial gadolinium injection. Note that a standard study will be performed 10 minutes after contrast injection. The ceCMR images were extremely reproducible (Figure 4). There was decreased variability between ceCMR scans as compared to the two SPECT scans. Therefore, we see that ceCMR produces high image quality, is highly reproducible in the range of 10-30 minute post intravenous bolus, and comparable to nuclear imaging. In addition, there is an excellent pathologic correlation for infarct size with this imaging technique.

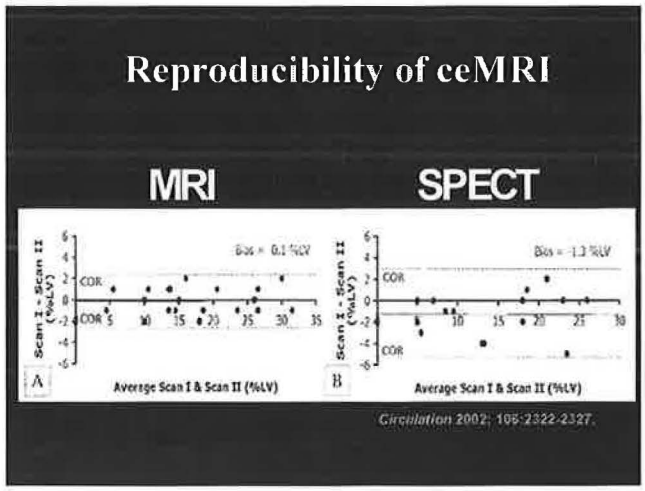


Figure 4. Both MRI and SPECT are reproducible in the assessment of infarct size. The reproducibility of MRI appears better than SPECT.

**Applications of ceCMR—Etiology of Heart Failure**

Thousands of patients present annually with clinical heart failure. In many of these patients the etiology may not be evident from initial history and clinical examination. This leads to a variety of chemical, serologic, and imaging tests that are performed. This imaging is performed not only to determine etiology but also to identify reversible causes of left ventricular dysfunction and have important implications in defining advanced therapy such as ICDs. Myocardial infarction results in subendocardial or transmural scar identified as bright areas by ceCMR. In some patients with cardiomyopathy due to other etiologies, ceCMR may not show any evidence of enhancement or may have different patterns of hyper enhancement. These patterns include mid wall stria or focal areas of increased uptake.

Because of these different patterns of increased uptake of myocardium, McCrohon and colleagues performed gadolinium enhancement studies in 90 patients with heart failure. The patient population included 63 patients with dilated cardiomyopathy with unobstructed coronary arteries and 27 patients with significant coronary artery disease at angiography and prior myocardial infarction (5). Fifteen patients without cardiomyopathy or known coronary disease were studied. In the control group there was no evidence of delayed enhancement. The average ejection fraction of patients with dilated cardiomyopathy was 39% and the ejection fraction of those with ischemic left ventricular dysfunction was 33%. Right ventricular ejection fractions were similar between the two groups at 45% and 48%, respectively. The degree of gadolinium enhancement as well as the location of enhancement was noted in the patient population. All 27 of the patients with ischemic left ventricular dysfunction had evidence of endocardial contrast enhancement consistent with prior myocardial infarction. The patients with dilated cardiomyopathy demonstrated 3 different patterns of delayed enhancement. In 37 of the 63 patients, no evidence of delayed enhancement was noted. Eighteen of the 26 patients who had enhancement had mid wall enhancement or striae. Eight of the patients had delayed enhancement confined to the endocardium and appeared indistinguishable from the patients with underlying coronary artery disease. It is believed that the mid wall enhancement is related to focal segmental fibrosis seen in some patients at autopsy. Pathologic findings in this population can range from mild to severe diffuse fibrosis or segmental fibrosis. The isolated mid wall abnormality in some patients with dilated cardiomyopathy is consistent with the pathologic finding of focal segmental fibrosis. The observation of endocardial myocardial enhancement in some patients with dilated cardiomyopathy raises the question of whether these patients may have had a prior myocardial infarction but in the setting of non obstructive coronary artery disease. Alternatively, some patients with dilated cardiomyopathy have pathologic evidence of endocardial and transmural fibrosis which is not distinguishable for myocardial infarction. When you examine both this study and other studies that have examined this issue, one can look at the sensitivity, specificity, and accuracy of Q Waves, regional dysfunction and contrast enhancement for determining ischemic etiology. Results from one study are shown in Figure 5. In this study, delayed enhancement is far superior in comparison to regional dysfunction or Q waves for determining etiology in a heart failure population.

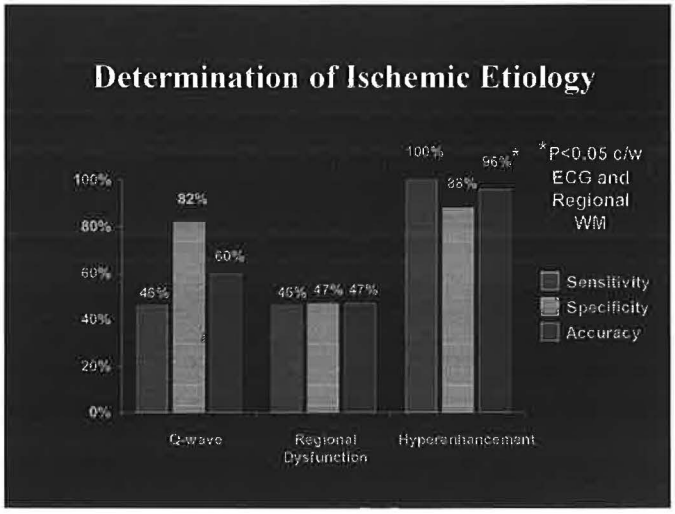


Figure 5. Sensitivity, specificity, and accuracy for determination of ischemic etiology in patients with heart failure,

Importantly, all patients with ischemic cardiomyopathy demonstrated endocardial fibrosis. This technique, therefore, may be a useful first approach to evaluating the patients who present with cardiomyopathy and might be applied with the following clinical rationale: Patients who undergo ceCMR who have no evidence of subendocardial fibrosis are unlikely to have evidence of significant coronary disease on catheterization. In these patients, there would be no need to perform stress testing, nuclear testing, or catheterization unless they had other symptoms prompting these studies. Patients with subendocardial scar identified on CMR would deserve additional testing to determine etiology. It would be anticipated that this strategy would rarely miss a patient with coronary artery disease (low false negative rate) but recognizes that some patients with subendocardial scar will not have obstructive coronary artery disease (modest false positive rate).

## Applications of ceCMR—Myocardial Viability

Determination of myocardial viability is an important issue in coronary disease since left ventricular viability predicts improvement in left ventricular function following revascularization procedures such as percutaneous coronary interventions and bypass grafting. Because of its association with improved outcomes following revascularization multiple imaging methods have been developed to determine myocardial viability. The gold standard has been PET imaging looking for matched perfusion and metabolic defects in a dysfunctional area. Other imaging methods to assess for the presence or absence of viability include rest redistribution studies from thallium imaging, markedly reduced wall thickness on transthoracic echocardiographic imaging, and contractile reserve using Dobutamine echocardiography. While all of these techniques have a role in assessment of myocardial viability they all have limitations in terms of predicting functional recovery following surgery or percutaneous intervention. The ideal imaging method would be able to not only identify viable from non viable myocardium but also

have an excellent correlation with outcomes including survival and recovery of function after revascularization or pharmacologic therapy.

The methodology used in quantitation of viability includes examining multiple sectors of the left ventricular wall following delayed contrast studies (Figure 6). This is an example of a picture of the myocardium where a clear hyperenhanced segment is seen. The diameter of the hyperenhanced segment is measured and compared to the diameter of the non enhanced area and a proportion of the wall that is viable is calculated. This can be calculated based on area of normal and abnormal myocardium as well. This methodology has gained standard acceptance and is used in almost all studies of delayed enhancement in the CMR literature. We will examine the use of this methodology in patients who have had coronary artery disease in both acute and chronic presentations and compare it to other imaging methodologies.

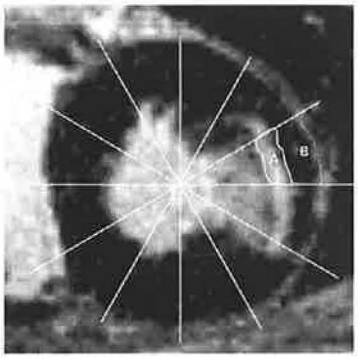


Figure 6. A sample delayed enhancement image with a viable area (b) and a nonviable area (a).

The first study includes application of this viability measurement in patients who have had a first myocardial infarction and were successfully revascularized (8). In this series 24 patients presented with myocardial infarction and underwent CMR. They later had a second CMR looking for wall motion improvement. The degree of transmural extent of hyperenhancement was calculated for each segment as 0%, 1-25%, 26-50%, 51-75% and 76-100%. The degree of hyperenhancement was then compared to wall motion improvement. In this population those patients without hyperenhancement were highly likely to have significant improvement in wall motion post revascularization. There was a graded effect between transmural hyperenhancement to no hyperenhancement (Figure 7). Patients who have 76-100% of their wall demonstrating enhancement are highly unlikely to have wall motion improvement. Thus, there appears to be a relationship between recovery of left ventricular function and the transmural extent of hyperenhancement in the acute setting.

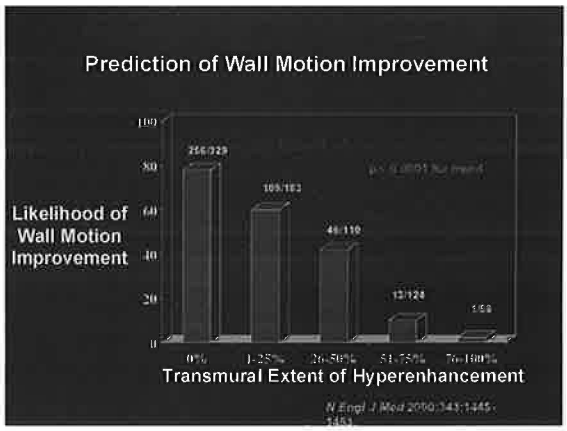


Figure 7. Relationship between transmural extent of hyperenhancement and likelihood of wall motion improvement in patients with acute myocardial infarction and salvage revascularization.

Hibernating myocardium is defined as viable but dysfunctional myocardium that is insufficiently perfused. In a small series 50 patients with left ventricular dysfunction who were scheduled to undergo revascularization for chronic coronary artery disease were studied (9). The protocol consisted of cine and ceCMR for viability followed by angioplasty or coronary artery bypass surgery within a month of the initial study. Repeat CMR was performed 3 months after the procedure. The results of this study appear very similar to the acute setting. The transmural extent of hyperenhancement is inversely associated with the likelihood of wall motion improvement. In this particular patient population, patients with hyperenhancement greater than 50% of wall thickness are unlikely to demonstrate improvement in wall motion following revascularization (9). Based on this study and others, the 50% threshold has been established as a cut off for significant viability.

Many of the CMR studies for viability have been performed in a small number of patients by a single group of investigators. A recent publication by a different group addressed the issue of delayed enhancement in patients undergoing coronary artery bypass surgery (10). This protocol consisted of preoperative, early post operative, and late post operative CMR images. Just as in the Kim article (9), there was a correlation between viability and improvement of left ventricular function postoperatively. Importantly, gadolinium MR studies remain fairly stable and show little change in the infarct zone over time. The authors noted a slight increase in area of delayed contrast early post op consistent with peri operative ischemia or infarction. The size of these new hyperenhanced areas decreased on the followup study suggesting that not all hyperenhacement represents scar.

In addition to recognizing the relationship between myocardial viability and ultimate improvement in function by CMR, it is important to understand the relationship between this methodology and other available techniques. PET imaging has been the gold standard for evaluating viability. One small series of 31 patients with chronic

coronary disease and left ventricular dysfunction were imaged by both CMR and PET (11). All patients had ejection fractions below 35%. The sensitivity for detecting scar tissue was 96% for the patient, 86% if you look at a simple myocardial segment, with a specificity of 100% for the patient and 94% for the segment. Despite these results 55% of segments with sub endocardial contrast enhancement by CMR were actually normal by PET. This suggests that some segments that have had underlying prior infarction will be identified as normal by PET.

Since not all centers have the capability of performing PET scanning, nuclear technology has become a popular technique in the evaluation of viability. In a nuclear scan the amount of viability is determined by the amount of tracer activity present in a myocardial segment. By CMR, however, we can determine not only the amount of viability (non enhanced area) but also the amount of scar (enhanced area)(Figure 8). In the schematic one can see that in nuclear we compare the infarcted area (a) to the remote area (b) whereas using CMR we compare the infarcted area (a) to the infarcted plus the non infarcted area. Both animal and human data are available using comparing ceCMR to SPECT imaging.

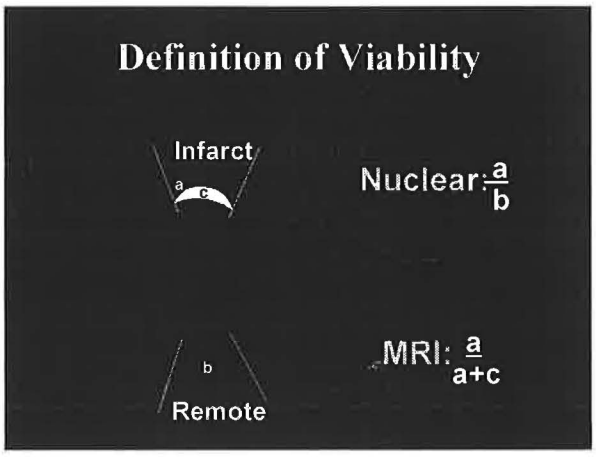


Figure 8. Definition of viability by nuclear and MRI represent different concepts as shown.

In a series of 15 dogs, the percent infarct was compared by histology, ceCMR, and SPECT (12). In this study the best correlation was between histology and ceCMR with a less robust relationship between SPECT imaging and histology (Figure 9). In a group of 90 patients the size of the infarct was compared by ceCMR and SPECT (12). Of note, there was an excellent agreement between the two methods for patients that have extensive scar but at smaller degrees of myocardial infarction cardiac MR is more likely to detect smaller areas of infarction than is SPECT (Figure 10).

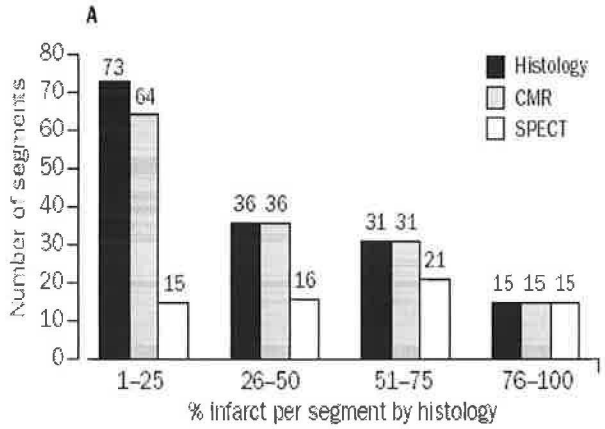


Figure 9. The relationship between histology, CMR, and SPECT in dogs with infarction is shown. The correlation is better for histology and CMR than for histology and SPECT (12).

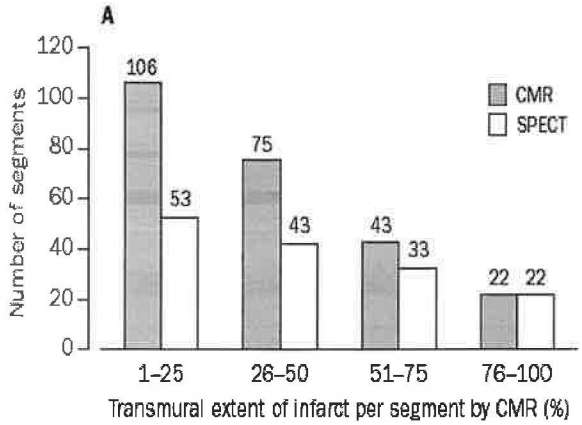


Figure 10. The relationship between the transmural extent of infarct is compared by CMR and SPECT. Note that the correlation is strong for greater extent of infarct but weaker at small infarct extents (12).

## Wall Thickness

Measuring resting wall thickness on transthoracic echocardiography is another way to determine viability. Wall thickness less than 6 mm is felt to represent nonviable myocardial tissue. Several investigators have felt that this very thin wall excludes the need to expose patients to additional tests of viability. The group at Duke is in the process of exploring the importance of viability assessment in patients with thin walls. This ultimately begs the question of how we should define viability. Viability may be defined as the absolute amount of myocardium, the extent of viable myocardium, or to the transmural extent of viability.

Thirty patients with large area of wall thinning underwent ceCMR. These patients averaged 62 years old, predominantly male, and had traditional cardiac risk factors including hypertension, diabetes, hypercholesterolemia, and premature coronary artery disease. They had markedly reduced ejection fraction (30%), and thin myocardial zone with a circumferential extent of the left ventricle of 22%. While the thin walls only demonstrated a viable thickness of 1.9mm, the transmural extent of viability was 41% on average. The zones with transmural extent of viability greater than 50% had increased likelihood for increasing wall thickness and contractile function after revascularization. In summary, akinetic myocardium may have a limited amount of infarction. Revascularization of akinetic regions may be associated with improvement in contractile function and reverse remodeling. Assessment of the transmural extent of viability using ceCMR can identify this reversible condition.

**Applications of ceCMR—Administration of Beta Blockers to Heart Failure Patients**

Beta blocker therapy is now associated with remodeling of the left ventricle including a decrease in chamber dimensions and improvement in systolic function (13). A clinical response may also be observed as an improvement in overall functional capacity. Patients do not respond uniformly to beta blocker therapy. To further address the heterogeneous response to beta blockers, 45 patients with chronic heart failure who were not candidates for revascularization were studied (14). They had an ejection fraction of less than 35% and were on stable medical therapy but not on beta blockers. Twenty eight of these patients had ischemic cardiomyopathy and 17 had idiopathic dilated cardiomyopathy. Typical ceCMR was performed. These patients were then treated with beta blocker therapy. Those patients with minimal areas of hyper enhancement had a greater likelihood of improvement of overall wall motion than those with larger areas of hyper enhancement.

**Applications of ceCMR—Hypertrophic Cardiomyopathy**

Hypertrophic cardiomyopathy is a diverse genetic disorder resulting in heart failure symptoms and sudden death in some patients. Sudden death may be predicted by clinical variables such as personal history of sudden death or syncope, family history of sudden death and marked increase in wall thickness.

The pathologic abnormality includes myofibrillar disarray with increase collagen substrate. Given the increased collagen matrix, this led to the hypothesis that patients with hypertrophic cardiomyopathy may have abnormalities on ceCMR (15). Evidence of fibrosis is typically seen at the insertion sites of the right ventricle and the septum (16). In the accompanying CMR image evidence of fibrosis and scarring is seen in the same locations. Contrast enhanced CMR has been performed in several small series. In a single patient with clinical and pathologic correlation, the contrast enhancement appears to be more related to the degree of collagen and scarring than to the degree of myofibrillar disarray (17). In a group of 53 patients, 79% had evidence of delayed enhancement (18). Patterns of hyperenhancement ranged from ventricular junction,

diffuse septal, subendocardial, and multi focal. Delayed enhancement was more likely to be seen in patients with progressive disease and in those with 2 or more risk factors for sudden death. This study was insufficient to explore the relationship between pattern of hyperenhancement and the risk of sudden death. Further studies will be needed to determine the strength of the relationship between ceCMR and those who will develop sudden death as well as who should be a candidate for electrical device therapy.

## CMR Clinical Program and Research at UT Southwestern

Scanners are equipped at Meadows, Rogers and St. Paul to perform clinical CMR studies. We currently perform approximately 50-60 studies per month with a target for growth of 80 studies per month over the next year. In addition to contrast enhanced studies, we perform scanning to examine pericardial disease, aortic pathology, pulmonary hypertension, arrhythmia substrate, congenital abnormalities, and abnormal coronary arteries.

The Dallas Heart Prevention Study is funded by the Reynolds Foundation. This epidemiological study of patients in Dallas County has included nearly 3000 CMR studies. These studies have been evaluated for heart function, heart size, aortic compliance, aortic atherosclerosis and other cardiac parameters. Many of these patients succumb to graft arteriosclerosis; therefore, we are exploring the incidence and distribution of contrast enhancement in this population. In addition, estimates of left and right ventricular function may be suboptimal with standard echocardiography. We are examining the relationship between quantitation of heart size and function by echocardiography and cardiac magnetic resonance in cardiac transplant patients.

Another population undergoing evaluation includes patients with pulmonary hypertension. These patients develop right heart dilation and dysfunction in response to pulmonary hypertension. Quantitation of the degree of dysfunction and the magnitude of dilation are important prognostic factors. We are examining these parameters as well as estimates of pulmonary artery compliance and delayed enhancement in this population.

## Summary

In summary, ceCMR is a quick and simple technique. Results from the test are reproducible, and it can be performed at many centers. There is a direct relationship of images to pathology. Many current and potential applications of ceCMR in the patient with heart failure exist. These applications range from determining prognosis, etiology and decision making and are likely to expand as our understanding of the use of CMR increases.

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**Selected web sites for more information on CMR:**

www.mrisafety.com
www.scmr.com

**Text book:**

Cardiovascular Magnetic Resonance. Warren J. Manning and Dudley J. Pennell, eds. Churchill Livingstone; New York, New York, 2002.