Usefulness of Delayed Enhancement by Magnetic Resonance Imaging in Hypertrophic Cardiomyopathy as a Marker of Disease and Its Severity

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"Regions of myocardial injury, acute myocardial infarction, chronic scar and fibrosis exhibit higher signal intensity than normal myocardium on T1-weighted MR images following administration of gadolinium based contrast agents."

The maximal contrast between the enhanced myocardium and the normal myocardium after 8-10 minutes from injection.

Rehr, Am J Cardiol 1986
Ts cholakoff, Radiology 1986
Eichstaedt, 1986
What is Delayed Enhancement?

**Gadolinium-DTPA is an extracellular contrast media**

It freely distributes in the interstitium but is unable to cross the intact cell membrane.
What is Delayed Enhancement?

Tissue volume of normal myocardium is:
- Cellular for 75-80%
- Interstitial for 10-15%
- Vascular for 5-10%

Polimeni PI. Am J Physiol 1974

Gadolinium Kinetic in normal myocardium
What is Delayed Enhancement?

The mechanism of DE in is a combination of:

- delayed wash-in and wash-out kinetics of nonviable tissue
- acute and chronic disarrangement of interstitium
- different volumes of distribution of Gd in viable and nonviable tissue

In Chronic Scar and in non ischemic fibrosis

Marholdt, Eur Heart J 2002
What is Delayed Enhancement?

In myocardial scar, the % of interstitium in the myocardial volume is increased
The wash out of Gd is slower

![Graph showing normal myocardium and myocardial scar/fibrosis](image)
• Inversion Recovery Gradient Echo (IR-GRE), in which the initial 180° inversion pulse (TI 250-350 msec) greatly increases the T1 weight of images.
• 8-20 min after intravenous injection of 0.1-0.2 mmol/kg of Gd-based contrast media.
• Image acquisition in a time window of 5 to 30 min after contrast administration, provided that the TI is adjusted.
Delayed Enhancement in Hypertrophic Cardiomyopathy

MRI with DE technique allows detection and quantification of macroscopic myocardial scar in HCM

Correlation between DE and scar at histology

Moon, JACC 2004
Kwon et al studied with DE-MRI 60 HCM pts before septal myectomy

Good correlation was found between DE and histology for the fibrosis score:

- no DE in 22/60
- mild DE in 33/60
- moderate DE in 4/60
- severe DE in 1/60
- no fibrosis in 19/60
- mild fibrosis in 33/60
- moderate fibrosis in 8/60

Kwon, JACC 2009
Delayed Enhancement in Hypertrophic Cardiomyopathy: prevalence

In 30 HCM patients MRI examination with DE technique was repeated a mean of 3±1 years.

At first MRI 23/30 (76.7%) patients had myocardial enhancement.
At the second MRI 28/30 (93.3%) had enhancement.

Aquaro et al, submitted
Delayed Enhancement in Hypertrophic Cardiomyopathy

- Diffuse Hyper enhancement
  - Trans-septal: 7%
  - RV septal: 7%

- Confluent Hyper enhancement
  - Ventricular junction: 23%
  - Multifocal: 17%
  - Subendocardial: 4%

Heterogeneity of pattern

Moon et al, JACC 03
In HCM as in other Cardiomyopathy is also present a mild enhancement: "subliminal enhancement", often in the typical site of hyper enhancement.

Heterogeneity of signal intensity

Aquaro et al, Am J Cardiol 2010
Delayed Enhancement in Hypertrophic Cardiomyopathy

Heterogeneity of fibrosis in myocardial disease:

**Replacement fibrosis**
- macroscopic scar
- microspic scar

**Plexiform fibrosis, associated to disarray**

Hasegawa, 1994

**Perivascular fibrosis**

**Increased connective tissue of myocardium**
(peri cellular, intercellular, and fascicular connective tissue).

Anderson et al, J Pathol 1979
Quantification of Delayed Enhancement in Hypertrophic Cardiomyopathy

Method of quantification:

Hyper enhancement as SI >2 SD + mean of Remote myocardial ROI
Hyper enhancement as SI >5 SD + mean of Remote myocardial ROI
Hyper enhancement as SI >6 SD + mean of Remote myocardial ROI
Hyper enhancement as SI>6 SD + mean of background ROI

Bondarenko demonstrated low accuracy in ischemic scar detection of 2 SD (JCMR 2005)

Spiewak, demonstrated that a fixed cut off of 6 SD was more accurate than lower cut off (eur radiology 2010)

SI of nulled myocardium does not follow a Gaussian distribution!
Quantification of Delayed Enhancement in Hypertrophic Cardiomyopathy

SI of nulled myocardium derives only from signal noise (background)

Average SI and SD of nulled normal myocardium should be the same of background

Rician distribution

Average Concordance in normal patients: 92.2 ± 2.3%
Quantiﬁcation of Delayed Enhancement in Hypertrophic Cardiomyopathy

Distribution of noise in MRI image is Rician and it could be approximated to a Rayleigh curve:

$$p(m|\sigma) = \frac{2}{(\sigma \sqrt{2})^{2K}(K-1)!} m^{2K-1} e^{-\frac{m^2}{2\sigma^2}}$$

- $m =$ signal
- $K =$ number of phase array coils
- $\sigma =$ SD of Background

From the SD of Background, the ideal curve of distribution of normal myocardium could be obtained.

SI distribution of enhanced myocardium differs from Rayleigh.

Aquaro, JCMR 2010
Aquaro, JCMR 2010

SD2 method

SD6 method

RC method

Area under intersection
Rayleigh curve
Myocardial signal distribution curve

Healthy patient

Concordance: 93%

n. of SD above the mean SI of myocardial-ROI

Relative distribution of SI

Original image  SD2 method  SD6 method  RC method

Aquaro, JCMR 2010
Aquaro, JCMR 2010

Average Concordance in HCM: 63±12.2%

Concordance: 69%

SD2 method
RC method
SD6 method

HCM Patient

Original image  SD2 method  SD6 method  RC method

Area under intersection
Rayleigh curve
Myocardial signal distribution curve

Relative distribution of SI

n. of SD above the mean SI of myocardial-ROI
Patients with 5y follow up and >40 years

Progressive disease:
- decrease in maximal LV wall thickness >5mm
- increase in LV end-systolic dimension >5mm
Delayed Enhancement and cardiac function in Hypertrophic Cardiomyopathy

- NYHA Class
  - % of Patients with DE
    - I: 40, II: 50, III/IV: 80
    - p=0.05

- NYHA CLASS
  - NYHA I
  - NYHA ≥II
  - P<0.002

- EF
  - EF≥50%
  - EF<50%
  - P<0.001

- % LV Mass With LGE
  - Overall p<0.001

Maron MS
Circ Heart Failure 2008

Aquaro
Am J Cardiol 2010

Olivotto
Am J Cardiol 2010
100 HCM patients
(70 males, mean age of 46±16 years)
Delayed Enhancement, arrhythmias and prognosis in Hypertrophic Cardiomyopathy

\[ *p=0.002 \]

<40 years

Moon, JACC 2003
Delayed Enhancement, arrhythmias and prognosis in Hypertrophic Cardiomyopathy

Prevalence of Arrhythmias on 24-h Holter ECG With Respect to DE

![Bar chart showing prevalence of arrhythmias in presence and absence of DE.]

- NSVT: p < 0.0001
- Couplets: p = 0.001
- PVCs: p = 0.007
- SVT: p = 0.07

Adabag et al, JACC 08
Delayed Enhancement in Hypertrophic Cardiomyopathy

A) Normal myocardium (non-enhanced voxel)

B) Macroscopic scar, (predominantly enhanced voxel)

C) Microscopic scar

Diffuse, plexiform fibrosis

Aquaro et al, Am J Cardiol 2010
Delayed Enhancement, arrhythmias and prognosis in Hypertrophic Cardiomyopathy

Aquaro et al, Am J Cardiol 2010
Delayed Enhancement, arrhythmias and prognosis in Hypertrophic Cardiomyopathy

Aquaro et al, Am J Cardiol 2010

Hyper
Mild
Normal

Chosen!
Delayed Enhancement, arrhythmias and prognosis in Hypertrophic Cardiomyopathy

Prediction of Non Sustained Ventricular Tachycardia

At multivariate Mild-enhancement was the only independent predictors of VT

Plexiform fibrosis associated to disarray is considered more arrhythmogenic than gross scar.

Aquaro et al, Am J Cardiol 2010
202 pts with HCM were studied with DE-MRI

111 (55%) were DE+

Follow-up of 1.9 years was performed

11 events (5 SCD, 2 appropriate firing, 4 heart failure)

not significant difference in annual event rate for DE+ vs DE- (5% vs 3%)

Short duration Follow-up!!!
424 pts with HCM were studied with DE-MRI

239 (56%) were DE+

Follow-up of 43±14 months was performed

4 SCD + 4 appropriate ICD firing + 2 Heart failure death

all these 10 pts were DE+, P=0.01 versus DE-

Rubinshtein et al, Circ Heart Fail 2010
Delayed Enhancement, arrhythmias and prognosis in Hypertrophic Cardiomyopathy

Kaplan-Meier Survival Curves:
Cardiac Mortality

Kaplan-Meier Survival Curves:
Sudden Cardiac Death

220 pts with HCM were studied with DE-MRI

DE+ 148 (67.2%)

Follow up of 1090 days

20 death (16 cardiac death) + 2 appropriate ICD firing

20/22 asymptomatic
only 3/22 had risk factors

Bruder et al, JACC 2010
Delayed Enhancement, arrhythmias and prognosis in Hypertrophic Cardiomyopathy

<table>
<thead>
<tr>
<th>No Cardiac death</th>
<th>Cardiac Death</th>
<th>p value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGE</td>
<td>65.2 (133)</td>
<td>93.8 (15)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**SCD risk factors**

- Maximal wall thickness 30 mm: 3.4 (7) vs. 6.3 (1), p = 0.46, OR = 1.88 (0.22-16.27)
- History of spontaneous VT: 4.9 (10) vs. 12.5 (2), p = 0.21, OR = 2.77 (0.55-13.90)
- Family history of SCD: 4.4 (9) vs. 6.3 (1), p = 0.54, OR = 1.44 (0.17-12.18)
- Unexplained syncope: 4.9 (10) vs. 12.5 (2), p = 0.21, OR = 2.77 (0.55-13.90)
- LVOT obstruction 30 mm Hg: 12.2 (22) vs. 13.3 (2), p = 1.00, OR = 1.10 (0.23-5.23)

**Number of SCD risk factors**

<table>
<thead>
<tr>
<th></th>
<th>No Cardiac death</th>
<th>Cardiac Death</th>
<th>p value</th>
<th>OR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>76.5 (156)</td>
<td>68.8 (11)</td>
<td>0.54</td>
<td>0.68 (0.22-2.04)</td>
</tr>
<tr>
<td>1</td>
<td>19.6 (40)</td>
<td>18.8 (3)</td>
<td>1.00</td>
<td>0.95 (0.26-3.48)</td>
</tr>
<tr>
<td>2</td>
<td>2.9 (6)</td>
<td>6.3 (1)</td>
<td>0.38</td>
<td>2.20 (0.25-19.48)</td>
</tr>
</tbody>
</table>

The presence of DE was the only significant predictor of the primary outcome.

DE did not reach statistical significance for predicting SCD.

Bruder et al, JACC 2010
217 pts with HCM were studied with DE-MRI, DE+ 136 (63%)
Follow up of 3.1 years

<table>
<thead>
<tr>
<th>primary end point</th>
<th>40 pts</th>
<th>34 DE+</th>
<th>6 DE-</th>
</tr>
</thead>
<tbody>
<tr>
<td>cardiac death</td>
<td>9 pts</td>
<td>8 DE+</td>
<td>1 DE-</td>
</tr>
<tr>
<td>unplanned cardiovascular admission</td>
<td>29</td>
<td>24 DE+</td>
<td>5 DE-</td>
</tr>
<tr>
<td>SVT/FV</td>
<td>9</td>
<td>8 DE+</td>
<td>1 DE-</td>
</tr>
</tbody>
</table>

appropriate ICD firing 2

DE- O’Hanlon et al, JACC 2010
# Delayed Enhancement, arrhythmias and prognosis in Hypertrophic Cardiomyopathy

Complexively, 1063 HCM patients followed-up for a mean of 2.9 years

<table>
<thead>
<tr>
<th>Study</th>
<th>n. of patients</th>
<th>n.DE+ (%)</th>
<th>End-point</th>
<th>End-point DE+</th>
<th>Endpoint DE-</th>
<th>SCD DE+</th>
<th>SCD DE-</th>
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<tbody>
<tr>
<td>Maron MS, Circ Heart Fail 2008</td>
<td>202</td>
<td>111 (55%)</td>
<td>11</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Rubinshtein, Circ Heart Fail 2010</td>
<td>424</td>
<td>239 (56%)</td>
<td>10</td>
<td>10</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Bruder, JACC 2010</td>
<td>220</td>
<td>148 (67%)</td>
<td>22</td>
<td>22</td>
<td>0</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>O’Hanlon, JACC 2010</td>
<td>217</td>
<td>136 (63%)</td>
<td>40</td>
<td>34</td>
<td>6</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td><strong>total</strong></td>
<td><strong>1063</strong></td>
<td><strong>634 (60%)</strong></td>
<td><strong>83</strong></td>
<td><strong>73 (88%)</strong></td>
<td><strong>10 (12%)</strong></td>
<td><strong>30 (88%)</strong></td>
<td><strong>4 (12%)</strong></td>
</tr>
</tbody>
</table>

- 88% of primary endpoint in DE+
- 88% of SCD in DE+
Recent studies suggested a role of DE as an independent predictor of adverse cardiac outcomes but are not conclusive.

A large, prospectively designed multicenter study is still needed to definitively establish DE as a predictor of SCD in HCM.

Results of European CMR registry.

DE is related to ventricular function and clinical status of the patients.

Methods for detection and quantification of DE need to be standardized.