Noninvasive Evaluation of the Myocardial Substrate of Cardiac Amyloidosis by Gadolinium Cardiac Magnetic Resonance

Enrica Perugini MD, Claudio Rapezzi MD, Tommaso Piva MD, Ornella Leone MD, Letizia Bacchi Reggiani BS, Letizia Riva MD, Fabrizio Salvi MD, Luigi Lovato, MD, Angelo Branzi MD, Rossella Fattori MD

\textit{a} Institute of Cardiology, University of Bologna, Ospedale S.Orsola-Malpighi, Bologna, Italy
\textit{b} Department of Radiology, University of Bologna, Ospedale S.Orsola-Malpighi, Bologna, Italy
\textit{c} Department of Pathology, University of Bologna, Ospedale S.Orsola-Malpighi, Bologna, Italy
\textit{d} Department of Neurology, Ospedale Bellaria, Bologna, Italy

\textit{Running Head:} Gadolinium CMR in cardiac amyloidosis

Corresponding author:

Enrica Perugini, MD
Università di Bologna
Istituto di Cardiologia, Ospedale S.Orsola-Malpighi
Via Massarenti 9, 40138 Bologna, Italy
Tel.: +39 051349858, Fax: +39 051344859
E-mail address: e_perugini@hotmail.com
ABSTRACT

Objective: to investigate prevalence and distribution of gadolinium enhancement at cardiac magnetic resonance (Gd-CMR) in cardiac amyloidosis (CA) patients, and look for associations with clinical, morphological and functional features.

Patients and Design: Twenty one patients with definitely diagnosed CA (immunoglobulin light-chain amyloidosis: transthyretin related, 9:12) underwent Gd-CMR.

Results: Gd enhancement was detected in 16/21 (76%) patients. Sixty six of 357(18%) segments were enhanced, more often at mid-ventricular level. Transmural extension of enhancement within each patient significantly correlated with left ventricular (LV) end-systolic volume ($r = 0.58$). Number of enhanced segments correlated with LV end-diastolic volume ($r = 0.76$), end-systolic volume ($r = 0.6$) and left atrial size ($r = 0.56$). Segments with enhancement in >50% transmural extension more often were severely hypokinetic or akinetic ($p = 0.001$). Patients with >2 enhanced segments showed significantly lower 12-lead QRS voltage and Sokolow index. No relation was apparent with any other clinical, morphological, functional or histological characteristics.

Conclusion: Gd enhancement is common but not universally present in CA, probably due to expansion of infiltrated interstitium. The segmental and transmural distribution of the enhancement is highly variable, and midventricular regions are more frequently involved. Enhancement appears to be associated with impaired segmental and global contractility and larger atrial size.

Key words: magnetic resonance imaging, gadolinium, amyloidosis, cardiomyopathies
Amyloidosis is a rare disease characterized by extracellular accumulation of fibrillary proteins, leading to loss of normal tissue architecture. Cardiac involvement—in the form of cardiac amyloidosis (CA)—is rather frequent and is an adverse prognostic marker[1]. On cardiologic grounds, the two most clinically relevant types of amyloidosis are 1) acquired monoclonal immunoglobulin light-chain amyloidosis, characterized by clonal plasma cells in the bone marrow which produce the immunoglobulin lights chains of the fibrillary deposit; and 2) the hereditary, transthyretin-related form of amyloidosis, which is caused by mutant transthyretin, a transport protein mainly synthesized by the liver.

Gadolinium cardiac magnetic resonance imaging (Gd-CMR) has been utilized for non-invasive evaluation of the myocardial substrate in ischemic, dilated and hypertrophic cardiomyopathies,[2][3][4][5][6][7] myocarditis,[8] and storage diseases.[9][10] As an extracellular fluid tracer, Gd accumulates in expanded interstitial space without crossing intact cell membranes.

We previously reported on the use of conventional CMR in the diagnosis of CA.[11] Gd-CMR could provide relevant additional information to help understand CA on pathophysiologic and morphological grounds, since the amyloid deposits induce marked interstitial expansion. To this end, we investigated the prevalence and distribution of Gd-CMR enhancement in patients with CA, and looked for associations with clinical, morphological and functional features.

**METHODS**

**Eligibility criteria**

All patients with a definite diagnosis of CA under observation in our Institute between December 2002 and January 2004 were prospectively studied with Gd-CMR. Inclusion criteria for the study were: 1) histologically proven systemic amyloidosis; 2) echocardiographic diagnosis of cardiac involvement. The latter was defined as end-diastolic thickness of the interventricular septum >1.2 cm (in the absence of any other cause of ventricular hypertrophy) plus two or more of the following echocardiographic findings: a) homogeneous atrioventricular valve thickening; b) atrial septal thickening; c) sparkling appearance of the ventricular septum.[12] Exclusion criteria were: 1) evidence of atherosclerotic coronary artery disease, based either on coronary arteriography or on pathologic inspection of hearts (after transplantation or death); 2) history of myocardial infarction. All patients received complete clinical assessment, 12-lead electrocardiogram echocardiography, and Gd-CMR. All patients provided prior written informed consent for this study involving Gd MRI, and for anonymous publication of data. The study was planned and performed in line with the principles of the Helsinki Declaration.

**Echocardiography**

Echocardiograms were obtained using a Hewlett Packard Sonos 5500 echocardiograph with multifrequency phased array probe. Bidimensional and Doppler technique were performed. M-mode measures were obtained according to the recommendations of the American Society of Echocardiography.[13] Early (E wave) and late (A wave) peak left ventricular (LV) filling velocities, E/A ratio and E wave deceleration time were measured from the trans mitral-pulsed Doppler velocity recordings, with the sample volume positioned at the tips of mitral valve leaflets. Restriction was diagnosed when the following criteria were satisfied: 1) deceleration time < 150 msec; 2) E to A wave velocity ratio > 2.5.[14]
Electrocardiogram
Electrocardiograms were obtained and analyzed for standard characteristics and for total 12-lead QRS voltage, defined as the sum of the amplitude of QRS complexes from the peak of the R wave to the maximal dip of S or Q wave, whichever was greatest in precordial and limb leads.[15]

Gd-CMR protocol
CMR images were acquired with a 1.5 T scanner (Signa Horizon, GE Medical Systems, Milwaukee, WI, USA) using a cardiac phased array coil. Coronal, transaxial, and two-chamber views were obtained as scout images. Breath-hold cine MR sequence with steady-state free precession by FIESTA (Fast Imaging Employing Steady State Acquisition; GE Medical Systems) was performed, covering the whole LV in short axis plane, from apex to atrioventricular ring, and in four-chamber view. The sequence parameters were as follows: repetition time, 4 msec; echo time, 1.7 msec; flip angle, 45°; matrix, 256 x 192; field of view, 320 mm; section thickness, 7 mm without spacing, NEX 1. Gadopentate dimeglumine (Magnevist, Schering, Berlin, Germany) (0.2 mmol/kg) was administered i.v. at 4 ml/sec. After a 10–15 min delay, a segmented inversion recovery fast gradient echo sequence (IR-FGE) was performed in the short-axis plane of the LV and in four-chamber view—identical to those used for FIESTA—with slice thickness of 7 mm, and gap of 0 mm. Repetition time of 5.3 msec; echo time of 1.3 msec, flip angle of 20°, matrix of 256 x 160, NEX 2, field of view of 320 mm were used. Optimal inversion times to null the normal myocardial signal were determined for each patient (230–400 msec, median 280).

Gd-CMR image analysis
Cine CMR images were evaluated by using an image analysis workstation (Advanced Windows 4.0, GE Medical Systems). Ventricular volumes, LV ejection fraction, parietal thicknesses and mass, inter-atrial septal thickness and left atrial diameter were measured by tracing epicardial and/or endocardial borders manually with commercially available software (Mass Analysis Plus, Medis, Leiden, The Netherlands). The 17-segment model recommended by the American Heart Association was utilized for assessment of regional thickness, kinesis and Gd enhancement of the LV.[16] Segmental wall motion was visually assessed (kinetics score) as ‘0’ = normal, ‘1’ = moderate hypokinesis, ‘2’ = severe hypokinesis, ‘3’ = akinesis, and ‘4’ = dyskinesis. The transmural extent of hyperenhanced tissue within each segment was scored (Gd enhancement score) visually using a 5-point scale: ‘0’ = <1% no enhancement; ‘1’ = 1–25% (of the total thickness enhanced); ‘2’ = 26–50%; ‘3’ = 51–75%; ‘4’ = 76–100%.[2][3] Additionally, to provide semiquantitative characterization of both the perimetral and transmural extent of Gd enhancement, a global enhancement severity score was created: this was defined as the sum of the individual enhancement scores of all enhanced segments in each patient. Assessment of the right ventricle focused on maximal diastolic thickness of the wall and presence of Gd enhancement at this level.

Myocardial biopsies
All available myocardial biopsy samples were fixed by microwave irradiation for 5 min in 10% buffered formalin, processed in the microwave oven and paraffin-embedded. Multiple sections were histologically examined using standard hematoxylin-eosin, Mallory trichrome and Congo red stain to identify the presence of amyloid by green birefringence under polarized light.
The following variables were considered for assessment of amyloid deposits: localization (endocardial, interstitial and vascular), type of distribution (multifocal, diffuse) and pattern of deposition in myocardial interstitium (interstitial perimysial, interstitial nodular or mixed). The amount of amyloid deposits was classified using the following semiquantitative method: mild (<30% involvement of the tissue fragments); moderate (30–60%); severe (>60% involvement).[17] The entity of myocardial damage was classified as follows: mild (if myocytes showed hypertrophy, mild atrophy and mild sarcoplasmic vacuolization); moderate (thin myocytes compressed into focal areas and showing intense sarcoplasmic vacuolization); severe (widespread thin, compressed and fragmented myocytes).

**Statistical analysis**
Statistical analysis was performed using SPSS 11.0 statistical software (SPSS Inc, Chicago, IL, USA). Continuous variables were expressed as the mean ± 1 standard deviation (or median/range, when specified); categorical variables were expressed as percentages. Based on the available numbers, subgroups were compared using non-parametric tests (U-Mann Whitney or Kruskal-Wallis) or contingency tables, as appropriate. Spearman’s correlation coefficient was calculated to assess correlation between variables and linear regression analysis was performed. *P* values <0.05 were considered statistically significant.

**RESULTS**

**Patient population**
Twenty one patients satisfied the eligibility criteria. All patients completed the study protocol. Nine patients had immunoglobulin light-chain amyloidosis. Twelve had transthyretin related amyloidosis, nine carrying either Gln89 transthyretin mutation (*n* = 3), Lys54 (*n* = 1), Pro36 (*n* = 1), Ala49 (*n* = 2), or Leu68 (*n* = 2), and three having “senile” wild type transthyretin related amyloidosis. Relevant clinical, morphological and functional findings at the time of the study are summarized in Table 1.

**Prevalence and distribution of Gd enhancement**
Fig. 1 shows a representative example of Gd enhancement (accompanied by images obtained at conventional CMR and at subsequent histopathological examination). Gd enhancement was found in 16/21 patients, corresponding to a prevalence of 76%. Among the 357 LV and septal segments analyzed in the total population, 66 (18.5%) displayed Gd enhancement. The median number of enhanced segments per patient was 2 (range, 0–10; mean, 3.0±2.7). The transmural distribution of the Gd enhancement score[2][3] was variable among the 66 enhanced segments. The score was 1 in 13 segments (19%), 2 in 16 (24%), 3 in 4 (6%) and 4 in 33 (51%). According to the 17-segment model,[16] high enhancement scores (defined as 3 or 4) were most often recorded at the midventricular level (25/126, 20%), as compared with the basal (11/126, 9%) and apical (7/105, 6%) levels (*p* = 0.003).

Fig. 2 shows representative examples of the two main enhancement patterns (localized vs. diffuse) observed by us. Among the 16 patients who displayed Gd enhancement, the pattern was localized in 12 and diffuse in 4.

As regards the right ventricle, zones of subendocardial Gd enhancement were observable in 3 patients (all of whom also had LV involvement).
Table 1. Clinical, morphological and functional parameters in the overall patient population.

<table>
<thead>
<tr>
<th>Study population (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
</tr>
<tr>
<td>Males: females</td>
</tr>
<tr>
<td>AL</td>
</tr>
<tr>
<td>ATTR</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>NYHA class</td>
</tr>
<tr>
<td>I/II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>CMR parameters:</td>
</tr>
<tr>
<td>IVS thickness (mm)</td>
</tr>
<tr>
<td>LV mass (g/m²)</td>
</tr>
<tr>
<td>LV diastolic volume (ml/m²)</td>
</tr>
<tr>
<td>LV systolic volume (ml/m²)</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
</tr>
<tr>
<td>Echocardiographic indices</td>
</tr>
<tr>
<td>of LV filling</td>
</tr>
<tr>
<td>DT (msec)</td>
</tr>
<tr>
<td>Restrictive filling pattern (patients)</td>
</tr>
</tbody>
</table>

Influence of Gd enhancement on segmental contractility
Among the 357 segments, the kinetics score was 0–1 in 278 (78%) and 2–3 in 79 (22%); none of the segments was dyskinetic. Presence of Gd enhancement appeared to influence segmental dysfunction: kinetics scores >1 were found in only 19% (60/320) of segments with low enhancement scores (0–2) as compared with 45% (17/37) with high enhancement scores (>2) (p = 0.001) (Fig. 3).

Clinical, morphological and functional variables and Gd enhancement
Comparing patients with and without Gd enhancement, no significant difference was apparent in terms of age, NYHA class or etiology (of note, the number of enhanced segments in patients with the senile form was 0.6±0.5, as compared with 3.6±2.0 for immunoglobulin light-chain amyloidosis and 3.8±3.0 for the hereditary transthyretin-related form; p = 0.21). At subgroup analysis based on the median number of enhanced segments (≤2 vs >2), the variables that significantly differed between the two subgroups were total 12-lead QRS amplitude (117 ± 48 mV vs 83.6 ± 24 mV, p=0.047) and Sokolow-Lyon index (21 ± 10 mV vs 13 ± 3.5 mV, p=0.018), which were both lower among patients with >2 enhanced segments. We also looked for evidence of correlation between Gd enhancement and clinical/morphological/functional variables among patients with at least one enhanced
segment, considering number of enhanced segments and global enhancement severity score as independent variables. On CMR, global enhancement severity score correlated with LV systolic volume ($r = 0.58$, $p = 0.018$; Fig. 4), and number of enhanced segments correlated with the following parameters: end-systolic left atrium diameter ($r = 0.56$, $p = 0.024$; Fig 4), LV end-diastolic ($r = 0.764$, $p = 0.001$) and end-systolic ($r = 0.607$, $p = 0.021$) volumes.

Histological features and DE
Right ventricle endomyocardial biopsies were available from 15 patients (each of whom had 4–6 endomyocardial tissue samples obtained in the standard fashion from the right side of the interventricular septum). The principal findings are shown in Table 2. Notably, in all patients both the amount of amyloid and the global myocardial damage were always moderate or severe. Amyloid infiltration involved interstitium in all 15 (100%) patients, the subendocardial layer in 11 (73%) and intramural coronary vessel walls in 7 (41%). Inflammatory infiltrate was evident in 2 (13%) patients. No significant histological difference was observable between patients with and without Gd enhancement.

Table 2. Histological features of 15 patients with myocardial biopsy according to presence of Gd enhancement.

<table>
<thead>
<tr>
<th></th>
<th>Patients with myocardial biopsy ($n = 15$)</th>
<th>Myocardial enhancement ($n = 12$)</th>
<th>No Myocardial enhancement ($n = 3$)</th>
<th>Significance (enhancement vs. no enhancement)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount of amyloid deposit (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>moderate</td>
<td>10 (66)</td>
<td>7 (58)</td>
<td>3 (100)</td>
<td>$p = 0.49$</td>
</tr>
<tr>
<td>severe</td>
<td>5 (34)</td>
<td>5 (42)</td>
<td>0 (0)</td>
<td>$p = 0.49$</td>
</tr>
<tr>
<td>Localisation (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>endocardial</td>
<td>11 (73)</td>
<td>9 (75)</td>
<td>3 (100)</td>
<td>$p = 0.87$</td>
</tr>
<tr>
<td>interstitial</td>
<td>15 (100)</td>
<td>12 (100)</td>
<td>3 (100)</td>
<td>$p = 1$</td>
</tr>
<tr>
<td>vascular</td>
<td>7 (46)</td>
<td>5 (42)</td>
<td>2 (66)</td>
<td>$p = 0.89$</td>
</tr>
<tr>
<td>Global myocardial damage (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mild</td>
<td>1 (7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>$p = 1$</td>
</tr>
<tr>
<td>moderate</td>
<td>9 (80)</td>
<td>9 (75)</td>
<td>2 (66)</td>
<td>$p = 0.66$</td>
</tr>
<tr>
<td>severe</td>
<td>2 (13)</td>
<td>3 (25)</td>
<td>1 (34)</td>
<td>$p = 0.66$</td>
</tr>
</tbody>
</table>

DISCUSSION

This study of Gd enhancement at Gd-CMR extends our knowledge of myocardial involvement in systemic amyloidosis, revealing a relation between the myocardial substrate and ventricular function.
In our clearly-defined population of patients with immunoglobulin light-chain or transthyretin related amyloidosis bearing a consolidated echocardiographic diagnosis of CA, we found a
remarkably high prevalence of Gd enhancement (in about three-quarters of our patients), and an association with LV segmental dysfunction. This finding requires explanation in the light of our knowledge of the general rules of Gd accumulation and of the specific histology of CA. Gd is an inert extracellular agent that cannot cross intact sarcolemmal membranes. In the normal myocardium, where the tissue volume is predominantly intracellular, the distribution volume of Gd is normally very low and Gd enhancement is absent. When interstitial space expansion occurs, Gd concentration increases within myocardial tissue.[18][19] In CA, interstitial expansion occurs due to extracellular amyloid infiltration. Thus, interstitial Gd accumulation due to amyloid infiltration is a highly plausible explanation for the very high prevalence of Gd enhancement. Nevertheless, several other possible contributory causes must also be considered. For instance, diffuse Gd accumulation has been shown to occur following acute myocarditis due to interstitial expansion caused by the inflammatory infiltrate (a major inflammatory infiltrate was present in 2 of our 15 patients with available myocardial biopsy, both of whom showed Gd enhancement). Furthermore, we cannot completely exclude the possibility that amyloid surrounding the myocytes might damage the cellular membranes, allowing Gd to penetrate the intracellular space. Finally, since amyloid deposition frequently involves intramural arteries, leading to ischemia in the context of normal epicardial vessels,[20] Gd might also accumulate in necrotic scars. However, the possibility that interstitial or post-necrotic fibrosis could provide a myocardial substrate for Gd accumulation seems unlikely, since it was absent in each of the 15 patients for whom a myocardial biopsy was available.

Widespread interstitial accumulation of amyloid can also explain the diffuse pattern of Gd enhancement observed in a minority of our patients. Although infrequent, this pattern appears quite distinctive with respect to previous descriptions in other myocardial pathologies. For instance, patients with dilated cardiomyopathy and normal coronary arteries who show Gd enhancement can display either a focal subendocardial/transmural pattern indistinguishable from that of ischemic patients, or else longitudinal/patchy midwall enhancement outside the territory of a coronary artery, probably reflecting myocardial fibrosis.[5] In hypertrophic cardiomyopathy Gd enhancement is frequent (with focal or diffuse patterns).[6][7] Gd enhancement has also recently been reported in two storage myocardial diseases, namely glycogenosis[9] and Anderson-Fabry disease.[10] In the latter, the accumulation was mainly localized to the basal infero-lateral LV wall and was not subendocardial (interstitial fibrosis has been hypothesized as the substrate).

It remains to be explained why Gd enhancement was absent in about 80% of the ventricular segments, and was completely undetectable in 5 (24%) patients, all of whom had a definite echocardiographic and histological diagnosis of CA. These observations are somewhat surprising in a disease that is characterized by widespread myocardial infiltration by amyloid. We can only speculate that a widespread, uniform myocardial infiltration of amyloid could have precluded the localized differences in signal intensity, which is a prerequisite for the recognition of areas of Gd enhancement.

In the one other available study on Gd enhancement in CA, Maceira et al analyzed a series of patients with CA alongside a comparison group characterized by hypertensive cardiomyopathy.[21] Although 69% of the patients in the CA group showed late hyperenhancement, the phenomenon tended to be global and subendocardial. The discrepancy with the limited number of enhanced segments recorded in our patients could be explained by at least four considerations: 1) technical/procedural differences could have led to different levels of sensitivity; 2) our population contained a higher proportion of patients with etiology other than AL (hereditary transthyretin-related and senile type); 3) our patients
had less severe cardiomyopathies (restrictive physiopathology was not a diagnostic inclusion criterion); 4) more generally, the histopathological profile of cardiac amyloidosis appears to be highly heterogeneous, with variable impairment of the subendocardial and subepicardial layers and preservation of central portions of the myocardium, in the context of different histological patterns (nodular, reticular, etc.) [22] [23] [24].

As regards image quality, we very frequently encountered ‘suboptimal’ images with low signal/noise ratio, a phenomenon that has been previously reported in the context of amyloid infiltration of both myocardium and soft tissues.[11][25][26]. The mechanism underlying this characteristic low signal/noise ratio remains uncertain: loss of signal might depend on the compact and complex environment of the amyloid extracellular matrix and/or magnetic field nonuniformity due to decreased proton density.[25][26]

An additional aim of the study was to look for factors possibly related to Gd enhancement. A comparison of patients with and without Gd enhancement did not reveal any difference in the distribution of clinical, morphological and functional variables, perhaps due to the limited number of patients. We extended the search for relations between Gd enhancement and patient-related variables by assessing the extent of Gd enhancement. Since the enhancement pattern was not dense or ‘scar-like’, a perimetal evaluation did not seem appropriate. We therefore adopted a semiquantitative approach based on: 1) number of involved segments; 2) transmural extension within each segment, scored from 0 to 4. In addition, we devised a ‘global enhancement severity score’ for each patient by summing the enhancement scores of the various enhanced segments. The number of segments involved was very variable (maximum 10, median 2); the mid-ventricular segments were those most affected. Patients with more than two enhanced segments showed lower QRS voltage on electrocardiogram, with significantly lower total 12-lead QRS amplitude and Sokolow-Lyon index. This observation fits the interpretation that the Gd enhancement was predominantly due to interstitial amyloid infiltration—itself the classic explanation for electrocardiogram abnormalities in CA.

An interesting association was recorded between amount of transmural enhancement and segmental dysfunction: patients with more extensive transmural enhancement showed a higher prevalence of severe hypokinesia or akinesia (Fig. 3). Since amyloid deposition is extracellular, it should not interfere with the myocardial cells’ intrinsic contractile function. However, when deposition becomes widespread, the amyloid surrounding the myocardial cells can provoke ‘functional isolation’, thus interfering with the development of adequate systolic tension during ejection. An important role could also be played by myocardial ischemia due to amyloid infiltration of small arteries, a characteristic feature of CA. Among the 14 patients where enhancement was present, the ‘global enhancement severity score’ correlated with LV end-systolic volume (Fig. 4). This finding suggests that the Gd enhancement could be related to reduced contractility both at the segmental and the global LV level. As for LV diastolic function, no correlation was observable between Gd enhancement and echo-Doppler indices of LV filling. Nevertheless, left atrium size—a reflection of both systolic and diastolic LV function—did correlate with the number of enhanced segments. Lack of apparent correlation between LV mass and any index of enhancement extension could be explained by the small number of patients and/or their particularly high average LV mass.

A specific feature of the study was the availability of histological information for over half the population. The absence of observed relationships between Gd enhancement and histological features could seem puzzling, since Gd CMR explores the interstitium, which can also be investigated by histological analysis. However, biopsy specimens derive from casual
sampling of the right side of the interventricular septum and thus might not be representative of the overall myocardial infiltration. Furthermore, the presence of moderate–severe myocardial amyloid infiltration in all 15 patients could have hampered the recognition of interindividual variations in Gd enhancement.

**Study limitations**

It must be stressed that this mainly descriptive study did not have a diagnostic or strictly clinical aim. Instead, it was conceived to gain knowledge regarding the potential of Gd enhancement as a non-invasive descriptor of the myocardial substrate in CA. Analysis was limited by numbers, due to the rarity of amyloidosis. This factor might have impeded recognition of clinical, morphological and instrumental factors differences between the two subgroups. On technical grounds, it should be noted that the decision to focus on zones and patterns of Gd enhancement rather than on Gd kinetics could have led to an underestimate of the phenomenon (and indirectly also to suboptimal image quality). Similar considerations can be made regarding the image acquisition times (after 10–15 min delay, in line with standard procedures) in our Gd-CMR protocol: use of a much shorter delay (as innovatively employed by Maceira et al[21]) might have led to improve enhancement detection. As regards the right ventricle (where 3 of our patients had observable enhancement), it must be pointed out that for technical and anatomical reasons assessment of Gd enhancement is very difficult in this site.

**Conclusions**

Myocardial Gd enhancement appears to be a very common—albeit not universal—feature in both the transthyretin related and immunoglobulin light-chain forms of CA. The enhancement is probably largely due to variable expansion of infiltrated interstitium. Segmental and transmural distribution of the Gd enhancement appears to be highly variable, with the mid-ventricular regions being more frequently involved. Moreover, Gd enhancement appears to be associated with impaired segmental and global contractility and larger atrial size. Gd-CMR provides a unique opportunity for non-invasive study of amyloid myocardial infiltration and its pathophysiological consequences. Further studies should explore the clinical utility of Gd-CMR in CA, including the potential prognostic implications of these observations.

**References**

4. Beek AM, Kuhl HP, Bondarenko O, Twisk JWR, Hofman MBM, Van Dockum WG, Visser CA, Van Rossum AC. Delayed contrast-enhanced magnetic resonance imaging


**Acknowledgement.** We are grateful to Robin MT Cooke for writing assistance.

We declare no competing interests.
**FIGURE LEGENDS**

**Figure 1.** In a 43-year-old man with familial transthyretin related CA, conventional CMR using ‘black blood’ fast spin Echo (A) and ‘bright blood’ fast-gradient Echo (B) shows increased LV and right ventricle thickness. Gd CMR Inversion Recovery Fast Gradient Echo (C) also reveals a large transmural zone of strong, patchy hyperenhancement (arrowed); following combined heart and liver transplantation, myocardial histology (D) displayed diffuse amyloid deposition with characteristic green birefringence at Condo Red staining (inset) and an area of massive infiltration (arrowed) corresponding to the strong, patchy enhancement seen at Gd CMR.

**Figure 2.** Post-contrast Gd CMR images (segmented inversion recovery fast-gradient echo sequences in short-axis view) showing representative examples of the main enhancement patterns: A) Localized enhancement, mainly involving the posterolateral midventricular segment (small arrows); note that the non-enhanced myocardium is nulled by the inversion recovery pulse. B) Diffuse subendocardial enhancement (particularly evident at the posterolateral level), and C) diffuse, intense transmural enhancement observable throughout the entire ventricular section.

**Figure 3.** Association between Gd enhancement (score ≤2 vs >2) and segmental dysfunction (kinetics score ≤1 vs >1) among the 306 myocardial segments analyzed: segments with more extensive transmural enhancement showed a higher prevalence of severe hypokinesia or akinesia.

**Figure 4.** Linear regression analysis of correlation between left ventricular end systolic (LVES) volume at CMR and global enhancement severity score (top), and between end systolic left atrium diameter and numbers of Gd enhanced segments (bottom).
Noninvasive evaluation of the myocardial substrate of cardiac amyloidosis by gadolinium cardiac magnetic resonance

Enrica Perugini, Claudio Ravezzi, Tommaso Piva, Ornella Leone, Letizia Bacchi-Reggiani, Letizia Riva, Fabrizio Salvi, Luigi Lovato, Angelo Branzi and Rossella Fattori

Heart published online June 6, 2005

Updated information and services can be found at:
http://heart.bmj.com/content/early/2005/06/06/hrt.2005.061911.citation

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Metabolic disorders (1030)
- Hypertension (3006)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/