Translating Novel Imaging Technologies into Clinical Applications

Myocardial T1 Mapping in Pediatric and Congenital Heart Disease

Eugénie Riesenkampff, MD; Daniel R. Messroghli, MD; Andrew N. Redington, MD; Lars Grosse-Wortmann, MD

In addition to the depiction of anatomy and function, tissue characterization of the myocardium has emerged as an important asset of cardiac magnetic resonance (CMR). Among the tissue properties that are quantifiable by CMR is diffuse myocardial fibrosis. Diffuse fibrosis is regarded to be the common pathological pathway toward loss of myocardial function in many cardiac conditions, including congenital heart disease.1-4 As fibrosis seems to have a major role in myocardial failure and may be reversible,1-8 its assessment by CMR has the potential to transform the way we monitor and treat our patients.9 In this review, we describe the technical aspects of fibrosis quantification with CMR and outline past and potential applications in congenital and pediatric heart disease.

Pathogenesis and Clinical Relevance of Diffuse Myocardial Fibrosis in Pediatric and Congenital Heart Disease

Diffuse myocardial fibrosis, which is present to a varying degree in children with acquired and congenital heart disease, has been attributed to abnormal loading conditions, cyanosis, and genetic predisposition.1-3,10,11 Myocardial fibrosis manifests in the pressure-loaded left ventricle of infants and children with aortic stenosis and coarctation.1 In patients with tetralogy of Fallot right ventricular myocardial disorganization and interstitial fibrosis have been demonstrated histologically.2,12 Interestingly, right ventricular fibrosis not only occurs in late adult survivors, but is already present in infants with this condition.1-3 The changes in myocardial architecture observed with fibrotic remodeling can be detrimental to heart function: Fibrous endocardial thickening of the right ventricular infundibulum is a predictor of poor right ventricular function in patients after tetralogy of Fallot repair.3 In patients with tricuspid atresia myocardial fibrosis is associated with systolic ventricular dysfunction early in life.5,13

In addition to being a mediator of cardiac dysfunction, diffuse fibrosis is the substrate for electric instability and a risk factor for life-threatening ventricular arrhythmia.14 Antifibrotic drugs have produced mixed results with regard to attenuation of fibrosis. This may be because of the difficulty in selecting those patients who are most likely to benefit from treatment, given our limited understanding of the pathogenesis of fibrosis.8

T1 Mapping in the Heart

In contrast to late gadolinium enhancement imaging which detects patchy areas of scarring, T1 mapping targets diffuse fibrotic processes. Myocardium which seems healthy, that is, without regional scarring by late gadolinium enhancement, may still have an abnormal, elevated amount of diffuse fibrosis. While late gadolinium enhancement and diffuse fibrosis may represent different severities along a spectrum of fibrosis in certain conditions, they also occur independently of one another.15

The quantification of tissue fibrosis using CMR is based on T1 values: T1 is the time after which a tissue’s longitudinal magnetization has returned to 63% of its original value after an inversion or saturation pulse. This time constant is determined by the tissue composition and is reasonably tissue specific. In principle, T1 times are derived from a series of coregistered images, acquired at different stages of T1 recovery.3,16 The T1 recovery curve is obtained from a curve fit through signal intensities plotted versus time that has elapsed after the inversion or saturation pulse.8,16 A T1 map is a single parametric image in which T1 times of tissue voxels are reflected by signal intensities of corresponding pixels on an absolute scale (in milliseconds).8,16

The first T1 measurement in human hearts was performed in 1985 in patients with myocardial infarction.15 Based on a pulse sequence originally designed by Look and Locker in 1970,18 and building on work in the interim, the MOLLI (modified Look–Locker inversion recovery) sequence was introduced in 2004 and, with modifications, continues to be widely used.19-21 Shortened MOLLI (ShMOLLI), in use since 2010, is a modification of the MOLLI sequence which was introduced for patients who cannot perform long breath holds.22

Saturation recovery-based approaches (eg, saturation recovery single-shot acquisition or SASHA) to T1 mapping are different from inversion-recovery-based techniques in that the recovery curve is not influenced by the readout.23 They were first reported in humans in 2013.24,25 A combination of saturation and inversion recovery (saturation pulse prepared...
heart rate–independent inversion recovery or SAPHIRE) was introduced in 2013.36

A recent comparison of the 4 most widely applied T1 mapping sequences demonstrated superior precision (ie, reproducibility) for the inversion recovery sequences MOLLI20 and ShMOLLI,22 while SASHA23 and SAPHIRE29 were more accurate (ie, closer to the true T1).27 The accuracy of the MOLLI sequence for postcontrast T1 times can be improved by using a different acquisition scheme which accounts for shorter T1 times. This scheme ensures that the majority of data points are positioned into the shortened upslope of the longitudinal relaxation curves of blood and myocardium.31 For blood T1 measurements, the use of T1* is recommended.23,28

## T1 Times and Extracellular Volume

Several T1 mapping-derived parameters have been proposed as biomarkers of myocardial disease. Among these, native (noncontrast enhanced) T1 time and the extracellular volume (ECV) are shaping up as the most widely embraced parameters to characterize the degree of myocardial alteration. Excellent intraobserver, interobserver, and interstudy reproducibilities have been demonstrated for both.19,29

### Native T1 Times

Different tissues are characterized by their intrinsic normal T1 times, which may change with pathology. Native myocardial T1 time reflects the combined proton signal from myocytes and interstitium and is prolonged by increased collagen content (fibrosis). Other conditions leading to T1 prolongation include edema (as in myocardial infarction and acute myocarditis) and protein deposition (as in amyloidosis). In contrast, increases in lipid content (as in Fabry disease) and iron overload cause T1 shortening.9,30 In adults with severe aortic stenosis native T1 values correlate with the degree of biopsy-quantified fibrosis.31 Native T1 times are longer in patients with hypertrophic and dilated cardiomyopathy than in normal controls.32,33 However, the significant overlap between native T1 in health and disease prohibits its use in differentiating normal from abnormal in most conditions.30

### Postcontrast T1 Times

Outside of acute cellular necrosis, standard gadolinium-based contrast agents remain extracellular, and their accumulation in the myocardial interstitial space shortens myocardial T1 times. The degree of shortening is related to the expanse of the extracellular space. However, other factors than the degree of fibrosis affect postcontrast T1, including the type and dose of contrast given, the interval between injection and imaging (T1 times are shortest directly after injection and rise slowly thereafter), as well as the patient’s volume of distribution for gadolinium and renal clearance of gadolinium.34–36 For these reasons, isolated postcontrast T1 measurements are not the approach of choice for the assessment of fibrosis.5,36,37

### Extracellular Volume

ECV is now the most widely used marker of diffuse myocardial fibrosis.9 It is derived from pre- and postcontrast T1 in blood and myocardium, as well as the hematocrit,38 using the following formula39:

\[
ECV = (1 - \text{hematocrit}) \times \frac{1}{\text{postcontrast T1 in myocardium}} - \frac{1}{\text{precontrast T1 in myocardium}}
\]

One prerequisite of this approach is that the distribution of gadolinium among tissue barriers (ie, between blood and myocardium) has reached an equilibrium. This is most accurately achieved by a continuous slow gadolinium infusion.39 However, direct comparison of this approach with a bolus-only technique (dynamic equilibrium method) showed no significant difference of the resulting ECV.40 Reassuringly, ECV obtained using the bolus-only technique showed good agreement with histology.36 As the bolus-only approach is easier to integrate into the clinical work flow, it is now the preferred strategy.9 A reasonable time delay after contrast injection seems to be 15 minutes, producing the ECV values with best correlation with histology.36 It is important to note that the bolus and infusion techniques seem to be equivalent only with ECVs <0.4,40 which has to be taken into account in patients with a suspected high degree of fibrosis. Another method to determine the blood tissue partition coefficient and, from this, ECV uses relaxation rates (R1=1/T1) for blood and myocardium precontrast and serially postcontrast during the washout phase.41 The partition coefficient and from it ECV are derived from the slope of the ratio of tissue versus blood R1.

Importantly, similar to native T1 times, there is considerable overlap in ECV values between health and disease, with the exception of ECV in amyloidosis.42

### Technical Controversies and Considerations

Native and postcontrast T1 times vary with magnetic field strength, with higher values at 3 T as compared with 1.5 T.19 Further variability is introduced by inhomogeneities in hardware, gadolinium compound, scan protocols, and T1 mapping sequence used between institutions. As compared with native and postcontrast T1 times in isolation ECV seems to be more reproducible.5 Generally, a uniform approach to obtaining T1 times is imperative for the comparability of measurements across patients and institutions.9

Most published studies measured T1 times in diastole. Blood in coronary arteries and capillaries affects myocardial T1 times and ECV as the vessels course through the region of interest. As the coronary blood flow varies with the cardiac cycle, higher ECV values during diastole were found in some studies,41 albeit not without controversy.36 One of the most important confounders of T1-derived fibrosis measures arise from partial volume effects at the border between myocardium and blood (inplane and throughplane),42 and care must be taken to exclude the endocardium/blood interface from the analysis.44
As T1 mapping sequences are ECG-gated, they are vulnerable to varying cardiac cycle lengths during the acquisition. Respiratory motion introduces further misalignment, and breath holds should be performed whenever possible.

A more detailed discussion of technical issues including the differences between the various available T1 mapping techniques is beyond the scope of this review, and the reader is directed elsewhere.23

Regional Differences in T1 Within the Heart and Sex and Age Effects

Native T1 values have been reported to be higher in the interventricular septum compared with the free wall,29,36 although not without controversy.19 While no differences between T1 measurements in basal, mid, and apical short axis slices were noted in healthy volunteers,19 this may not hold true for pathological conditions.29,36 Therefore, at least 3 slices covering representative regions of the heart should be acquired. Caution is advised when performing T1 measurements in thin-walled structures such as the right ventricle or the atrium as they are more prone to partial volume effects at the blood/myocardium border which can lead to falsely elevated native T1 times. Measurements in the right ventricle and in the atrium have been reported, but histological validation is lacking.45–47 In adults, native T1 times and ECV increase with age.44 Several, but not all, studies report CMR fibrosis markers to be higher in women than in men.44,48 However, with normalization to blood T1 times, sex differences of native T1 times may disappear, possibly because of sex differences in hematocrit.45

Implementing T1 Mapping in Patients With Pediatric and Congenital Heart Disease

Several adjustments are necessary when applying T1 mapping to children to account for higher heart rates, increased artifacts from motion, and smaller anatomy: As the T1 signal needs sufficient time for recovery between the Look–Locker experiments, inversion recovery-based methods such as MOLLI need to be adjusted to accommodate the higher heart rates in children. As a rule of thumb, the interval between 2 inversion experiments should be no shorter than 5 times the maximum T1 in blood or myocardium. Shorter intervals carry the risk of underestimating long (such as native) T1 times because of incomplete recovery of longitudinal magnetization. Recent implementations of inversion recovery-based acquisition schemes (MOLLI, ShMOLLI) therefore allow for defining the pausing intervals as a function of time (eg, 3 seconds) rather than several heart beats. Figure 1 illustrates modifications of the MOLLI sequence and considerations for the choice of pausing schemes depending on the heart rate.

The spatial resolution must be adjusted to image smaller structures such as a neonatal heart or the thin-walled right ventricle. The maximum spatial resolution within the currently widely applied sequences is limited by their single-shot structure. A histologically validated technical solution exists for small animals (rats with approximate heart rates of 300 bpm) combining a segmented, inversion recovery-prepared Look–Locker-type pulse sequence with a multimodal reconstruction framework. Acceleration of data acquisition and reduction of motion artifacts are possible through temporal undersampling and radial nonbalanced steady-state free precession.49 This approach may become useful in infants with high heart rates. Another method with potential for pediatric and congenital indications was developed for the assessment of the right ventricle.50 This technique includes a segmented readout and uses compressed sensing to achieve the necessary spatial resolution at acceptable scan durations.

Motion artifacts from unreliable breath-holding and patient movement are particularly common in children. In addition, beat-to-beat variation of the heart rate leads to acquisition of source images at varying positions in the cardiac cycle. Thus, although modern T1 mapping software31 automatically generates parametric maps with color-coded T1 times (Figure 2), it may be necessary to derive T1 times using the source images with individually adjusted regions of interest instead. The smaller the region of interest and the greater the potential for respiratory and cardiac motion, the greater the benefit from deriving T1 times from these source images rather than the map.

CMR Fibrosis Markers in Clinical Pediatric and Congenital Heart Disease

The studies published to date in pediatric and congenital heart diseases are listed in the Table. Postcontrast T1 times and
tissue–blood partition coefficient were used at earlier stages of T1 mapping-based estimation of diffuse fibrosis but are inferior to native T1 times and ECV. In all studied pediatric and congenital heart disease populations, CMR fibrosis markers differed from controls. In most studies, T1-related markers of increased fibrosis were associated with decreased myocardial function or clinical status, suggesting that fibrosis may play a role in loss of cardiovascular health not only in adults but also in children with heart disease. In a group of adult patients with different forms of congenital heart disease left ventricular ECV correlated with left ventricular end-diastolic volume index and ejection fraction.15

In children and adolescents after tetralogy of Fallot repair postcontrast T1 values of the right ventricular anterior wall function of cardiac dysfunction and clinical status.

Table. T1 Mapping Studies Published To Date in Pediatric and Congenital Heart Disease

<table>
<thead>
<tr>
<th>Journal and Year of Publication</th>
<th>Author</th>
<th>No. of Patients Included</th>
<th>Age of Subjects, y</th>
<th>Native T1 Times, ms</th>
<th>Postcontrast T1 Times, ms</th>
<th>ECV</th>
<th>Myocardial Region Field Strength and Sequence Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circ Cardiovasc Imaging, 2010</td>
<td>Broberg et al15</td>
<td>Systemic RV (n=11)</td>
<td>36±14</td>
<td>Not reported</td>
<td>Not reported</td>
<td>35.0±5.8%</td>
<td>6 segments</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Repaired TOF (n=17)</td>
<td>34±12</td>
<td>Not reported</td>
<td>29.2±3.4%</td>
<td>33.7±5.6%</td>
<td>1 mid SA slice</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zyanotic CHD (n=10)</td>
<td>42±11</td>
<td>Not reported</td>
<td>31.4±3.2%</td>
<td>31.9±4.9%</td>
<td>1 mid SA slice</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other CHD (n=12)</td>
<td>33±12</td>
<td>Not reported</td>
<td>31.4±3.2%</td>
<td>24.8±2.0%</td>
<td>1 mid SA slice</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All CHD patients (n=50)</td>
<td>37±12</td>
<td>Not reported</td>
<td>31.4±3.2%</td>
<td>24.8±2.0%</td>
<td>1 mid SA slice</td>
</tr>
<tr>
<td>J Cardiovasc Magn Reson, 2013</td>
<td>Tham et al52</td>
<td>Children after anthracycline (n=30)</td>
<td>15±3</td>
<td>1155±57</td>
<td>20.7±3.6%</td>
<td>18 segments</td>
<td>1.5T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls (n=0)</td>
<td>Not reported</td>
<td>652±54</td>
<td></td>
<td>1 mid SA slice</td>
<td>Gd-Bolus</td>
</tr>
<tr>
<td></td>
<td>Plymen et al47</td>
<td>Systemic RV after Mustard/Senning (n=14)</td>
<td>24±7</td>
<td>Not reported</td>
<td>0.254±0.036</td>
<td>IVS</td>
<td>1.5T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls (n=14)</td>
<td>32 (24–49)</td>
<td>Not reported</td>
<td>0.230±0.032</td>
<td>IVS</td>
<td>1.5T</td>
</tr>
<tr>
<td></td>
<td>Kozak et al46</td>
<td>Repaired TOF (n=18)</td>
<td>13±3</td>
<td>Not reported</td>
<td>443±54</td>
<td>Not reported</td>
<td>1 mid SA slice</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls (n=12)</td>
<td>13±2</td>
<td>Not reported</td>
<td>510±77</td>
<td></td>
<td>1 mid SA slice</td>
</tr>
<tr>
<td>J Am Coll Cardiol, 2014</td>
<td>Dusenbery et al53</td>
<td>Aortic stenosis (n=35)</td>
<td>16 (1.7–27)</td>
<td>Not reported</td>
<td>0.27 (0.22–0.42)</td>
<td>6 sectors</td>
<td>1.5T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls (n=27)</td>
<td>16 (8–20)</td>
<td>Not reported</td>
<td>0.25 (0.18–0.27)</td>
<td>1 mid SA slice</td>
<td>Look-Locker</td>
</tr>
<tr>
<td></td>
<td>Riesenkampff et al54</td>
<td>HTX† (n=17)</td>
<td>13 (1.2–17)</td>
<td>Not reported</td>
<td>0.45±0.06*</td>
<td>LV lateral wall</td>
<td>1.5T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls (n=9)</td>
<td>12 (9–17)</td>
<td>Not reported</td>
<td>0.40±0.03*</td>
<td>1 mid SA slice</td>
<td>MOLLI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls (n=12)</td>
<td>Not reported</td>
<td>977±40</td>
<td></td>
<td>1 mid SA slice</td>
<td>Gd-Bolus</td>
</tr>
<tr>
<td></td>
<td>Parekh et al55</td>
<td>Cardiac dysfunction (n=3)</td>
<td>Overall age</td>
<td>982±30</td>
<td>Not reported</td>
<td>16 segments</td>
<td>1.5T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HCM (n=1)</td>
<td>15 (5–25)</td>
<td>Not reported</td>
<td>1021±35</td>
<td>SA images</td>
<td>MOLLI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls (n=12)</td>
<td>Not reported</td>
<td>1040±21</td>
<td></td>
<td>No Gd</td>
<td></td>
</tr>
</tbody>
</table>

Values are median (and range) or mean±SD. CHD indicates congenital heart disease; ECV, extracellular volume; FLASH-IR, fast low angle single shot inversion recovery; Gd, gadolinium; HCM, hypertrophic cardiomyopathy; HTX, heart transplantation; IVS, interventricular septum; LV, left ventricle; MOLLI, modified Look-Locker inversion recovery; RV, right ventricle; SA, short axis; SASHA, saturation recovery single-shot acquisition; and TOF, tetralogy of Fallot.

*Reported results represent tissue blood partition coefficient, not ECV.
†Three patients had repeated studies.
correlated with right ventricular end-systolic volume indexed to body surface area.46 Interestingly, left ventricular postcontrast T1 values were also abnormal, indicating, as animal studies have suggested, important cross talk between the ventricles. Patients with transposition of the great arteries and systemic right ventricle late after atrial redirection surgery had higher ECV in the interventricular septum as compared with controls, and ECV correlated with natriuretic peptide and cardiac index.47 In children and adolescents with congenital aortic stenosis, ECV correlated with the degree of diastolic dysfunction.48 Studies need to identify if an earlier intervention is able to prevent this chronic fibrotic burden, which is thought to ultimately affect myocardial function. In anthracycline-treated pediatric cancer survivors ECV was increased and correlated with decreased mass/volume ratio and decreased left ventricular wall thickness/height ratio, lower peak oxygen uptake during exercise, and higher cumulative anthracycline exposure.52 The authors of this study presumed that ECV may be a more sensitive indicator of early ventricular remodeling and precede detectable functional alterations. However, the suitability of ECV to identify patients at risk needs to be evaluated in longitudinal studies. Obese adolescents had higher ECV as compared with healthy volunteers, with the highest values in the obese with type 2 diabetes mellitus.56 Native T1 times and the tissue–blood partition coefficient were significantly higher in children after heart transplantation compared with controls, and correlated with diastolic dysfunction.54 In this study, the left ventricular free wall showed the most significant deviation from normal, which is in keeping with the notion that the left ventricular free wall is a predilection site of functional and structural changes, for example in Duchenne’s muscular dystrophy or dilated cardiomyopathy.57

The first multicenter normal values of native T1 times in adults have recently been published.48 The authors also published normal values for ECV, but had to assume the hematocrit for ECV calculation in 2 of 3 patients. Normal ranges for native T1 times and ECV in children have not been established. The requirement for intercenter collaboration to establish normal values but also to study populations with relatively rare conditions underscores the need for a uniformly accepted approach to measuring ECV, including image acquisition and postprocessing.

Future Directions

More work is needed to establish CMR markers of diffuse myocardial fibrosis in the clinical care of children with heart disease: ECV needs to be validated against histology and its reproducibility demonstrated, especially in the right ventricle. Its role as a prognostic marker must be shown. If successful, ECV and native T1 may become useful in the selection of patients for antifibrotic treatment with medications that interrupt the renin–angiotensin–aldosterone and other profibrotic pathways. There is evidence for a genetic predisposition to accelerated fibrotic remodeling.41 CMR could be used as a noninvasive surveillance tool for patients deemed to be at higher risk for adverse remodeling. Of note, children seem to have a much higher myocardial regenerative potential as compared with adults.55 This may imply that children benefit from antifibrotic treatment to a greater extent than older patients and that the early detection and treatment of diffuse fibrosis may alter their long-term disease trajectory.

Conclusions

The potential of cardiac T1 mapping to change our management of children with cardiomyopathies and patients of all age groups with congenital heart disease is tremendous. This technique is currently on the verge of moving from a research tool that provides pathophysiological insights to a clinical tool that is expected to identify patients who are at risk for myocardial failure or may benefit from antifibrotic treatment. The overlap between native T1 times and ECV in health and disease suggests that these parameters will be useful primarily for monitoring of disease progression and treatment, rather than for differentiating normal from pathological.

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