Increasing Productivity in Myocardial and Liver T2* Acquisition and Analysis

Juliano Lara Fernandes, M.D., Ph.D., MBA; José Michel Kalaf, M.D.

Jose Michel Kalaf Research Institute, Radiologia Clinica de Campinas, Campinas, Brazil

Parametric mapping has become one of the key developments in cardiovascular magnetic resonance (CMR) over the last years [1]. Despite more recent applications using T1 and T2 maps, T2* mapping was the first clinical driver of this growth and a landmark for the success of CMR on the assessment of iron overload in different diseases.

The clinical importance of CMR for this purpose was first pointed out in 2001 by Anderson et al. [2]. In this seminal paper, the authors demonstrated a clear association between values of myocardial T2* and left ventricular ejection fraction, identifying the cut-off of 20 ms as a marker of myocardial iron overload with a significant increase in risk of ventricular dysfunction below the 10 ms limit. At this time, they also correlated the values of liver T2* with direct liver iron concentration (LIC) as measured by invasive biopsy.

Since that initial paper, advances in T2* sequences and analysis gained rapid speed with important clinical information following through. In technical aspects, the first T2* sequences for both liver and heart used single echo and multiple breath-holds for the generation of images with different echo times. While providing acceptable interscanner and intercenter reproducibility, breath-hold times were up to 20 seconds and the total exam time was also very long due to the need for multiple respiratory pauses [3]. The first evolution of the method resulted in sequences that provided multiple echoes using a single respiratory pause and significantly shortened total exam time while keeping very good overall interscanner, interpatient and intercenter reproducibility [4]. Myocardial T2* was then further advanced by the use of black blood techniques that maintained the previous advantages of fast acquisition but reduced the coefficient of variation of the exam to 4.1% using diastolic acquisitions and removal of flow compensation allowing for lower initial TEs [5]. Finally, other organs started to be assessed along with the heart and the liver, with special focus on the pancreas and pituitary gland [6, 7].

In terms of clinical applications, more accurate calibration curves of liver T2* and liver iron content became available, allowing for precise determination of LIC [8, 9], comparable to previously validated T2 techniques [9]. Prognostic data started to identify cohorts of patients at high risk for development of heart failure showing that 47% of patients with a cardiac T2* below 6 ms developed heart failure at one year follow-up [10]. The calibration of cardiac T2* and true myocardial iron concentration (MIC) was made possible after the work of Carpenter et al. with twelve human hearts donated after patient's death or transplantation comparing CMR values to plasma atomic emission spectroscopy [11]. This work along with previous validation studies for the liver now permits the classification of severity in both organs using T2*, R2* and final LIC and MIC levels (Table 1).

The impact of T2* mapping along with the development of new iron chelators over the last decade has resulted in a major change in the natural history of thalassemia major and other transfusion-dependent anemias. In countries that applied CMR routinely for these patients along with regular access to chelation, early diagnosis of high MIC allowed for significant changes in management strategies. Reductions in overall mortality of up to 62% and iron overload related deaths of 71% were observed [12] with a shift of the major cause of death in these patients from heart to chronic liver disease and infections [13]. Currently, all major guidelines for the management of iron chelation recommend the use of both liver and myocardial T2* assessment on a yearly basis and

Table 1

	Classification	T2* (ms)	R2* (Hz)	Iron Concentration (mg/g dw)
Myocardial	Normal	≥ 20	≤ 50	≤ 1.16
	Mild/Moderate	10 to 20	> 50 – 100	> 1.16 to 2.71
	Severe	< 10	> 100	> 2.71
Liver	Normal	≥ 11.4	< 88	< 2.0
	Mild	3.8 – 11.4	88 – 263	2.0 – 7.0
	Moderate	1.8 – 3.8	263 – 555	7.0 – 15.0
	Severe	< 1.8	> 555	> 15.0

Reference values and stratification of liver iron concentration and myocardial iron concentration by T2* at 1.5T.

as the key diagnostic test for therapeutical strategies [14-16].

Clinical demand: Needs and limitations

Despite the very successful use of T2* mapping for the assessment of iron overload, recent surveys indicate that the adoptance of the technique has been very heterogeneous and that cases of high LIC and/or high MIC are still abundant, especially in developing parts of the world where most of the patients are located [17]. Understanding the limitations that do not allow widespread use of the technique is important in order to move the field further in the right direction.

The first limitation refers to the number of patients in need of the exam. While T2* mapping was initially developed for the study of patients with thalassemia major, it is now recognized that it also plays a significant role in the management of other diseases including myelodisplastic syndromes, sickle cell disease, hemochromatosis, thalassemia intermedia and other rare anemias with regular blood transfusions [18]. While the number of known patients with thalassemia major in the world is only just above 100,000 [19], the total number of patients counting all the other indications for iron overload assessment with MRI is estimated to be at least five times higher, especially with the increase in life span in most of these diseases. This puts significant pressure onto the healthcare system if one considers not only the costs but also the availability of slots in the current MRI installed base. For example, assuming that a standard scanner performs around 500 exams a month, it would require approximately 80 exclusively dedicated centers just to account for all the yearly scans needed to fulfill this unmet need of iron overload evaluation. Since scanners are not available exclusively for this purpose, these patients have to compete with demands from all other MRI indications, significantly limiting actual availability.

The second significant limitation to access is the need for dedicated training for the acquisition and assessment of T2* images of the liver and heart. While the pulse sequences used to generate the images are based on well-known gradient echo techniques, only recently have dedicated protocols been delivered as standard packages on most systems. Not only that, the post-processing step of quantitative analysis of the acquired images and T2* calculations is not automatic and frequently requires the use of a third party commercial software or spreadsheet [20]. Training is also necessary in the correction for some of the intrinsic limitations of the sequence, especially in situations of high LIC where truncation or use of an additional constant on the decay equation is needed [21, 22]. This additional toll results in many centers supposedly capable of performing the exam being unable to offer it on a routine basis, further reducing availability.

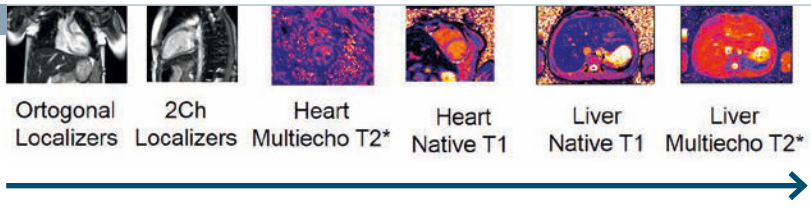
Considering the central role that CMR has taken in the assessment of iron overload together with the limitations discussed above, a new approach to improved productivity while maintaining the high quality of the exams was designed using recent product developments provided by Siemens Healthcare with the MyoMaps package.

All Iron Detected (AID) project

The AID project was developed in order to offer high quality iron overload assessment to the maximum number of patients with a clinical indication for the exam in a multicenter design. The idea was to overcome limitations of (1) cost, (2) availability, (3) need for extensive training and (4) low productivity. To reach these goals, the aim was to develop a CMR protocol where the patient would stay inside the magnet for not more than five minutes, with a total exam time of under ten minutes. This would allow for the evaluation of approximately 70 patients in a 12-hour shift, boosting productivity by 200% with an increase from two to six patients per hour. The protocol was applied in seven different centers in six cities in Brazil (Radiologia Clinica de Campinas, Mater Dei Hospital (Belo Horizonte), Santa Joana Diagnostico (Recife), Sirio Libanes Hospital (São Paulo), CDPI (Rio de Janeiro), DASA (São Paulo) and Ana Nery Hospital (Santa Cruz do Sul)). Three of these centers had very little experience with either T1 or T2* imaging and no specific training was provided except for a one-hour meeting for overall discussion of the project with the principal investigators four months prior to the implementation of the exams. The protocol was transferred to each center's scanner (two 1.5T MAGNETOM Aera scanners with software version *syngo* MR D13 and five 1.5T MAGNETOM Avanto scanners with software version *syngo* MR B17, Siemens Healthcare, Erlangen, Germany) using a prototype version of MyoMaps.

Figure 1 shows the protocol used in the study. While our focus was on T2* we added the assessment of native T1 of the heart and liver using MyoMaps as well for research purposes, actually prolonging the exam time for another one to two minutes but still keeping within the five-minute exam target. For the localizers we chose to use a traditional orthogonal setup followed by a simple 2-chamber prescription used for the positioning of the heart short axis slices.

1



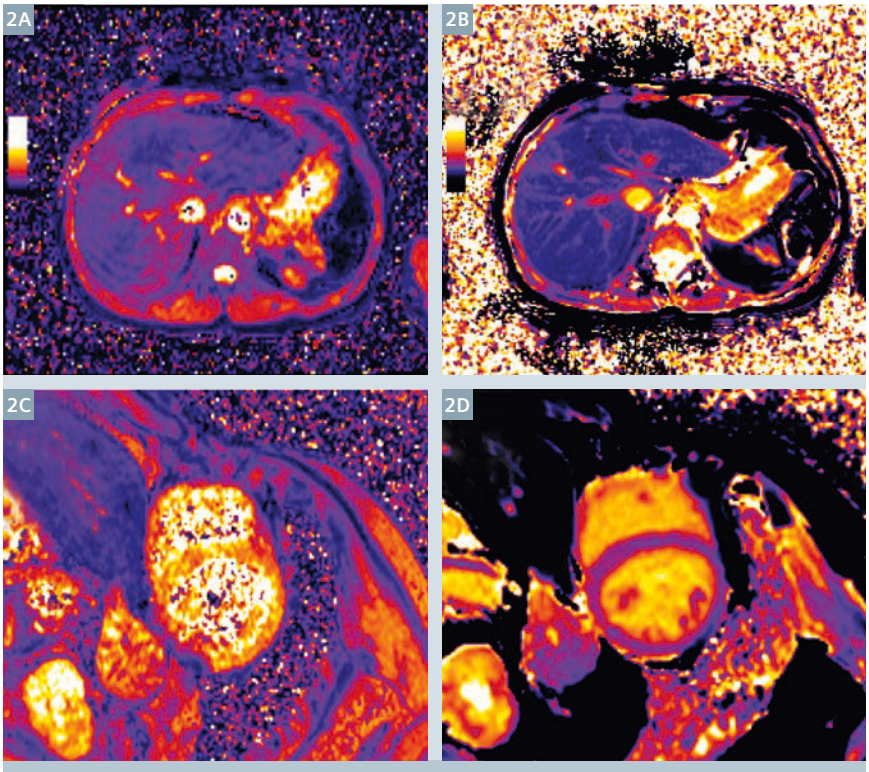
1 Overview of the protocol used in the AID project with the MyoMaps prototype[1] product.

Next, a multi-echo black-blood gradient echo sequence in the mid portion of the left ventricle acquired 12 short-axis images with different TEs (2.3 to 18.9 ms, with 1.5 ms intervals). The same short-axis slice position was copied in order to obtain eight images using a Modified Look-Locker Inversion Recovery (MOLLI[1]) sequence with 5 (3 s) 3 design as previously published for native T1 of the heart [23]. The same sequence was used for the axial single slice acquisition of the liver and also for T1 mapping. The position of the liver was copied for the final multi-echo gradient echo sequence consisting of twelve images with TEs from 1.1 to 11.0 ms with 0.9 ms intervals. As an optional acquisition, a complete set of ten short-axis slices covering the entire left ventricle was obtained in two centers that also performed a free breathing prototype cine sequence with sparsely sampled iterative reconstruction for rapid evaluation of left ventricular function in less than one minute.

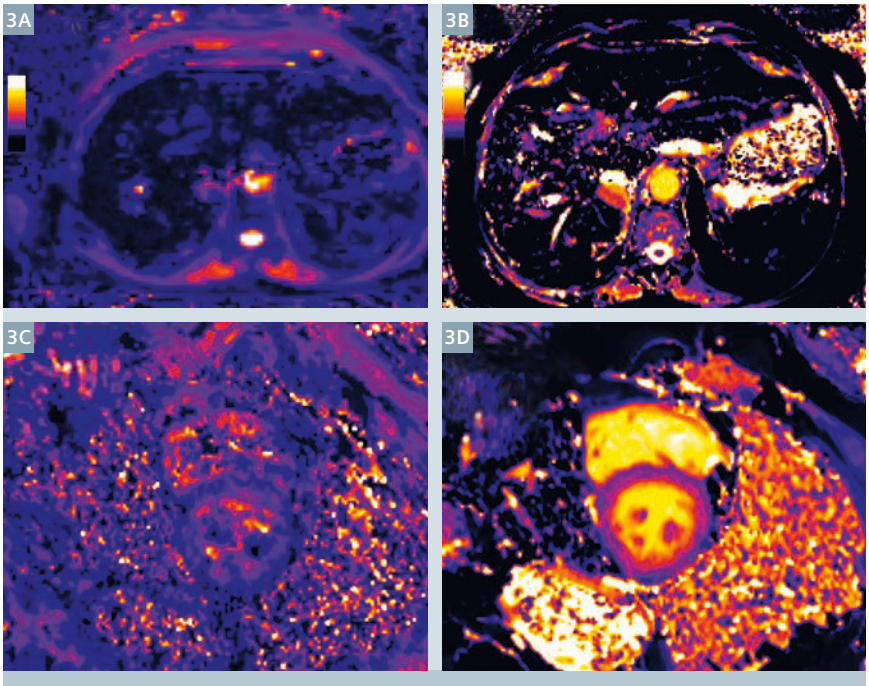
While special care was taken to acquire images in reduced time, we were also careful to guarantee that the results would be accurate and consistent among all centers, especially the ones with least experience. This was planned in the MyoMaps product by automatic application of Inline Motion Correction and pixel-based quantification of both T1 and T2* based on the raw images generated. Inline processing removed the need for further analysis of the images with additional post-processing reducing also the overall time for reporting the final values for both organs in addition to the shortened acquisition intervals. Furthermore, it also allowed us to avoid the need for training the different sites in manual analysis: This was skipped altogether, since previous results with inline processing showed good correlation between the automatic measures and manual analysis [24].

The preliminary results of the project allowed us to scan 179 patients with

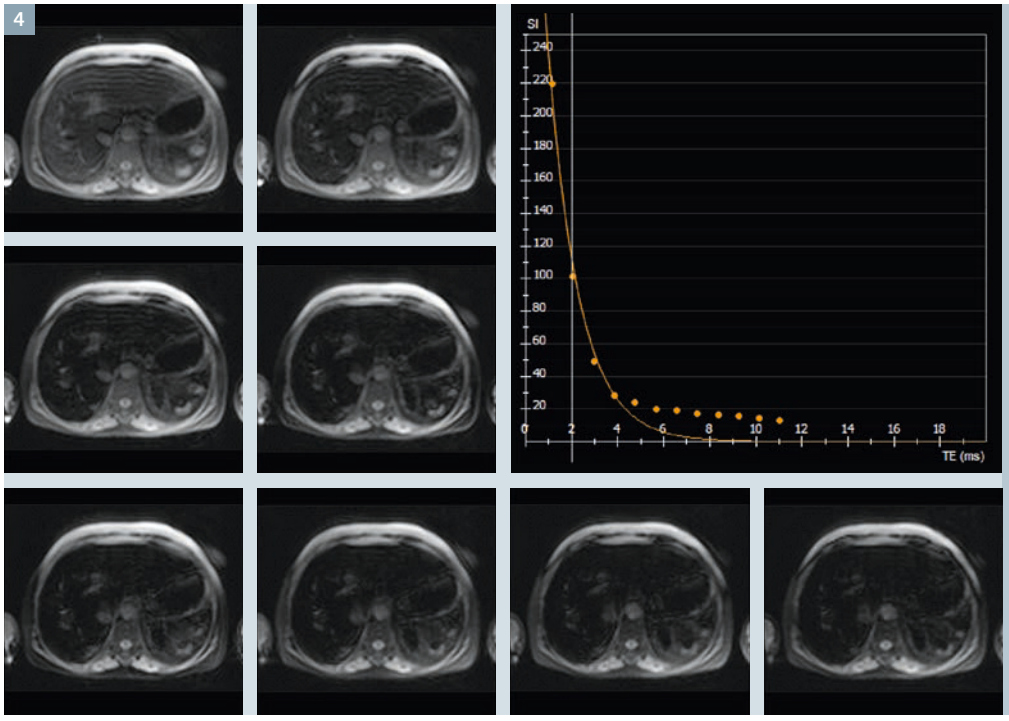
[1] WIP, the product is currently under development and is not for sale in the US and in other countries. Its future availability cannot be ensured.



2 Inline pixel fit images automatically generated for T2* and T1 of the liver **(2A, B respectively)** as well as the heart **(2C, D).** Both organs had normal T1 and T2* values in this 41-year-old female patient with sickle cell disease.



3 A 35-year-old female patient with severe iron overload in the liver and heart with a T2* of 1.7 ms and 9.8 ms **(3A, C respectively).** T1 values for both organs were also low calculated at 320 ms and 751 ms **(3B, D respectively).** The window and level used are the same as in figure 2 and demonstrate the differences in the color maps for both variables when assessing normal and pathological organs.



4 Original gradient echo raw images used for the inline calculation of the liver T2* map in figure 3 with the first eight images with different echoes represented. The manual post-processing fitting of the T2* decay curve with the truncation of the last points after the fourth dataset is also shown.

a median scan time of 5.2 minutes (IQR 4 to 7 minutes) in patients with a wide age range (2 to 91 years old, 44% children[2]/adolescents) and varying myocardial T2* values (4.2 to 61 ms) and liver T2* values (0.7 to 32.4 ms). An example of a patient with normal T1 and T2* values of the heart and liver is shown in figure 2. These images are automatically generated by the scanner as DICOM images and each pixel represents the calculated T1/T2* values without any need for further post-processing. Figure 3 shows severe iron deposition in the liver and heart. In figure 4 the first eight original raw images used for the offline calculation of the T2* of the liver are shown along a manual fitting curve that was used for the comparison with the inline generated T2* map. In this case, truncation had to be used to account for the plateau observed in the images with longest TEs after the fifth echo.

Further clinical applications

While T2* mapping of the heart and liver might apparently be limited only to assessment of iron overload, the technique has much broader potential clinical applications in which MyoMaps may provide significant insights. Blood oxygen level-dependent (BOLD) CMR has been proposed for almost twenty years as an accurate technique to assess myocardial perfusion [25]. In particular T2* imaging has been considered one of the most sensitive methods for this assessment as it is dependent on the paramagnetic properties of deoxygenated hemoglobin [26, 27]. However, previous studies used relatively simple imaging techniques and did not assess the myocardium with more current tools using parametric T2* mapping with higher resolution imaging and possible improvement in accuracy. The use of MyoMaps for stress-induced changes in BOLD CMR might be therefore helpful in this area [28].

Another potential use of T2* mapping also derives from previous observations of myocardial edema and hemorrhage characterized during the acute phase of myocardial infarction [29]. This also opens the possibility of using pixel-fit automatically generated images maps for identifying and monitoring tissue changes along different phases of the disease providing a roadmap for understanding physiological and pathological changes, which might influence treatment strategies.

Conclusion

In summary, T2* imaging with CMR has experienced significant technical advances over recent years and has been proven to positively affect the management of iron overload diseases. The use of the prototype MyoMaps package[1] with automatic motion correction and inline quantification of T2* as well as T1 and T2 allowed us to further increase productivity, decrease training needs and offer more exams to patients with high demand for these scans with total imaging time around five minutes. The application of T2* mapping with MyoMaps might allow us to investigate other aspects of cardiovascular disease using BOLD imaging and edema and hemorrhage characterization.

[1] WIP, the product is currently under development and is not for sale in the US and in other countries. Its future availability cannot be ensured.

[2] Siemens disclaimer: MR scanning has not been established as safe for imaging fetuses and infants less than two years of age. The responsible physician must evaluate the benefits of the MR examination compared to those of other imaging procedures.

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Contact

Juliano Lara Fernandes
R. Antonio Lapa 1032
Campinas-SP – 13025-292
Brazil
Phone: +55-19-3579-2903
Fax: +55-19-3252-2903
jlaraf@terra.com.br