T2* and T2 mapping of the spleen before and after SPIO administration: Correlation with liver function

Poster No.: C-0223
Congress: ECR 2010
Type: Scientific Exhibit
Topic: Abdominal Viscera (Solid Organs)
Keywords: spleen, liver cirrhosis, SPIO
DOI: 10.1594/ecr2010/C-0223

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Purpose

In chronic liver disease (CLD), iron overload is known as one of the causes to accelerate oxidative stress that induces fibrosis (liver cirrhosis) and hepatocarcinogenesis [1]. Previously, we have shown, utilizing T2* and T2 map of the upper abdomen, that as the liver function deteriorates, followings take place in patients with CLD: T2* values of the liver decreases, representing intrinsic iron overload and iron deposition in the liver. After superparamagnetic iron oxide (SPIO) is given, #T2* and #T2 values of the liver (difference between pre- and post-SPIO values) decrease, representing Kupffer cell dysfunction [2]. Figure 1 on page 2 illustrates the presumed mechanism of this phenomenon, and basic idea regarding the relationship between the size of iron particle and T2/T2* properties is shown in Figure 2 on page 3 [3-5]. This lead us to the next question how CLD affects the spleen in terms of T2* and T2 property in patients with CLD.

The purpose of this study, therefore, is to elucidate the features of the spleen on T2* and T2 maps before and after SPIO administration in correlation with the liver function level.

Images for this section:

![Figure 1: Presumed mechanism of iron metabolism in normal and cirrhotic liver. In normal livers, there is no iron deposition before SPIO administration. After SPIO is given, Kupffer cells with normal function can take up good enough amount of iron and forms large-sized iron deposits.](image-url)
clusters of SPIO, which can cause both T2* & T2 shortening: in cirrhotic livers, however, intrinsic iron is already present as a form of ferritin or hemosiderin, which may cause T2* shortening, but may not be sufficient in amount to cause T2 shortening at 1.5T. After SPIO is given, the amount of taken-up iron would be less and large-sized cluster may not be formed due to impaired Kupffer cell function. Thus, both T2* and T2 shortening effect caused by SPIO could be reduced in cirrhotic patients.

<table>
<thead>
<tr>
<th>Particle size</th>
<th>Extrinsinc iron</th>
<th>Intrinsinc iron</th>
<th>T2 vs T2*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small</td>
<td>Small-clustered SPIO ex) splenic RES, impaired KC</td>
<td>Ferritin</td>
<td>surface area ↑ T2 property &gt; T2* property</td>
</tr>
<tr>
<td>Large</td>
<td>Large-clustered SPIO ex) normal KC</td>
<td>Hemosiderin (including GGB)</td>
<td>susceptibility ↑ T2 property &lt; T2* property</td>
</tr>
</tbody>
</table>

RES = reticuloendothelial system, KC = Kupffer cell, GGB = Gamma-Gandy body in the spleen

**Fig. 2:** Relationship between the size of the iron particle and MR characteristics. Small-sized particles, namely small-clustered SPIO or ferritin, have large surface areas that would cause more prominent T2 than T2* shortening. Large-sized particles, including large-sized SPIO or hemosiderin, have more susceptibility effect that shortens T2* rather than T2.
Methods and Materials

1. Study population
Between January and November 2007, 103 patients were retrospectively recruited who underwent SPIO (ferucarbotran: Resovist, BayerSchering, Germany)-mediated MR imaging for suspected liver masses. There were 69 men and 34 women, with age ranging from 38 to 84 (mean 56) years old. As for viral background, 64 and 37 patients had hepatitis C and B, and 97 patients had none of them. 11, 29, 17, and 8 patients had normal, Child-Pugh grade A (CP-A), B (CP-B), and C (CP-C), liver function level. Exclusion criteria included 1) those with apparent history of transfusion or chronic intake of chalybeate or excessive alcohol; 2) those with images of poor quality due to artifacts; 3) those after splenectomy. Institutional review board approved this study waiving obtaining informed consent because of its retrospective nature.

2. MR examination
1.5T clinical units (Intera Achieva, Philips Medical Systems) were used for all examination. In addition to the usual scans, multi-slice multi-echo fast field-echo (mFFE) sequence and multi-echo turbo-spin-echo sequence (mTSE) were obtained both before and after SPIO to create T2* and T2 maps, respectively. Parameters for mFFE are as follows: TR/median TE/FA=256/26/28, body coil, EPI factor = 29 (#TE=1.8ms), FOV 40cm, matrix 126x144, thick/gap=5/0 mm, 10 slices (5-slice x2), scan time 48s (24s x2), under breath-holding. Those for mTSE are as follows: TR/1st TE/FA = 3000 - 4000/10/90, TSE factor 32, echo-space =10 ms, FOV 4, 0cm, body coil, matrix 256x176, thick/gap = 5/0 mm, scan time about 5 min with breath-triggering.
T2* map was generated from mFFE data with B0 correction using PRIDE software (Philips Medical Systems), representing T2* decay at each pixel (Figure 1 on page 5). T2 map was generated on the operating console, representing T2 decay at each pixel (Figure 2 on page 5).

3. Assessment
T2* and T2 values of the organ were measured by placing circular region-of-interest (ROI) on the maps. As large as an ROI as possible was placed within the spleen, avoiding vessels, masses, or apparent artifactual inhomogeneity, by referring to other images. At least 3 ROIs per slice for at least 3 slices were placed and the results were averaged. Thus, T2* and T2 values of the spleen before and after SPIO administration, and the difference between them as well, were correlated to liver function level.
Images for this section:

**Fig. 1:** Generation of T2* map

**Fig. 2:** Generation of T2 map
Results

1. **T2* values of the spleen**
   There were 65 patients available for analysis. First, we roughly divided the patients into preserved (11 normal and 29 CP-A) and impaired liver function (17 CP-B and 8 CP-C) groups. Before SPIO, T2* value of the former was 59.3±26.8 ms, whereas that for the latter was 65.2±30.2, showing no significant difference. After SPIO, however, T2* value of the former (24.7±7.9) was significantly larger than that of the latter (29.9±5.8) (p=0.009, unpaired-t test). The difference between before and after SPIO (#T2*) for the impaired function group (45.5±16.1) was higher than that of the preserved function group (34.7±17.7), but did not reach the statistically significant level (p=0.1).

   When the patients were divided into 4 groups, similar trend was confirmed (Figure 1 on page 6). As the liver function level deteriorates, T2* value of the spleen after SPIO decreases. There was no significant linear correlation between the groups and T2* values before SPIO or #T2*, however, there is a sudden drop at CP-C, which closely related to the incidence of Gamma-Gandy body (GGB), as identified on the conventional MR images. When CP-C group was excluded, correlation between them became significant for #T2* (rho=0.33, p=0.04).

   Representative cases are shown in Figure 2 on page 7.

2. **T2 values of the spleen**
   We first divided the 65 patients into preserved and impaired liver function groups. Before SPIO, T2 value of the former was 165.1±26.8 ms, whereas that for the latter was 159.6±15.2, showing no significant difference. After SPIO, however, T2 value of the former (96.6±27.9) was significantly larger than that of the latter (75.5±16.8) (p=0.05, unpaired-t test). #T2 for the impaired function group (84.8±16.1) was marginally higher than that of the preserved function group (68.5±17.7) (p=0.07, unpaired t-test).

   When the patients were divided into 4 groups, similar trend was confirmed (Figure 3 on page 8). As the liver function level deteriorates, T2 value of the spleen after SPIO significantly decreases and #T2 significantly increases. There was no significant correlation between the groups and T2 values before SPIO. There appears to be no correlation between the incidence of GGB and pre-SPIO T2 values. Representative cases are shown in Figure 4 on page 9.

Images for this section:
**Fig. 1:** Correlation between T2* value of the spleen and liver function level. T2* values after SPIO decreases as the liver function deteriorates. No linear relationship is observed for Pre-SPIO T2* and #T2*, however, there is a sudden drop at Child-Pugh grade C group that closely correlates with the incidence of Gamna-Gandy body.
Fig. 2: T2* value of the spleen without (Case 1) and with (Case 2) Gamna-Gandy body. Pre-SPIO, post-SPIO, and T2* values are all lower in Case 2 as compared to those in Case 1.
Fig. 3: Correlation between T2 value of the spleen and liver function level. T2 values after SPIO decreases, and ΔT2 increases as the liver function deteriorates. No significant relationship is observed for Pre-SPIO T2. There is no correlation with the T2 values and incidence of Gamma-Gandy body.
Fig. 4: T2 values of the spleen with normal (Case 1) and impaired (Case 2) liver function. Note pre-SPIO spleen appears brighter, and post-SPIO spleen appears darker in Case 2, as compared to Case 1. #T2 is much larger in Case 2 than in Case 1.
Conclusion

Signal intensities of the spleen in CLD before and after SPIO have been reported by several investigators, but the results were inconsistent and sometimes contradictory to each other [6-13]. Figure 1 on page 12 summarize the results of the major previous reports. The presumed biggest reason for this inconsistency is that the signal intensity on T2WI, T2*WI, and T1WI have all T2, T2*, and T1 components of various degrees, depending upon the parameter setting. Particularly, T1 shortening effect of intravascular SPIO may not be negligible. In this regards, direct measurement of T2* and T2 values is simply precise and therefore preferable. Another point is the different types of SPIO, namely ferumoxides and ferucarbotran, may have different T2* and T2 shortening effect, probably due to different particle size, dose, and clusterization characteristics [9].

Our data, using ferucarbotran as an SPIO agent and T2*/T2 values as indices, showed that there was no significant difference in T2* and T2 values of the spleen according to the liver function level. This may be explained as follows: as the liver function deteriorates in CLD, portal hypertension usually progresses. As a result, splenic congestion, and finally, intrasplenic tiny hemorrhage (becoming GGB) [15,16] may occur: the former causes more prominent T2 than T2* prolongation, and the latter causes more prominent T2* than T2 shortening. Degree of splenic congestion may also depend upon the development of collateral circulation. T2* and T2 values of the spleen may thus be determined according to the balance of these various factors, and therefore, the results may be inconsistent.

After SPIO is given, one clear result we obtained was that #T2 was elevated as the liver function deteriorates, suggesting increased uptake of SPIO by the splenic reticuloendothelial system (RES), possibly in compensation for the reduced SPIO uptake by the hepatic Kupffer cells. This may sound contradictory to the previous nuclear medicine report [14], stating increased splenic uptake of colloid radioisotope (RI) is due to increased volume of the organ but not to its increased function per unit volume. However, what should be noted is that ferucarbotran and colloid RI is different in nature. Ferucarbotran has been shown to be less likely trapped by splenic RES than ferumoxides, and possibly than colloid RI, due to its smaller size and less dose [9]. It is considered, therefore, that ferucarbotran may be fully taken up by splenic RES only when intravascular SPIO concentration is elevated, for example, in patients with liver cirrhosis. This phenomenon may be observed more clearly with T2 rather than with T2* values, because small-clustered SPIO in the splenic RES more effectively shorten T2 rather than T2*. When GGB is present, because pre-SPIO splenic T2* values is already substantially reduced, increased #T2* may not be appreciable. Figure 2 on page 12 shows the overall concept of this presumed mechanism.

In conclusion, T2* and T2 values of the spleen after SPIO administration were shown to be related to liver function level. As liver function deteriorates, the amount of SPIO taken up in the spleen may be increased, probably in compensation for the decreased SPIO
uptake in the liver. T2 values of the spleen may be more sensitive to this phenomenon than T2* values, because of the small-sized clustering of SPIO in the spleen. Presence of GGB may obscure this phenomenon, possibly due to marked T2* and moderate T2 shortening effect.

**Images for this section:**

<table>
<thead>
<tr>
<th>Author &amp; ref.#</th>
<th>SPIO</th>
<th>index</th>
<th>Cirrhotic spleen relative to non-cirrhotic spleen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>T2WI</td>
</tr>
</tbody>
</table>
| Hundt W, et al. [10]   | FMX | %ΔSNR | ↓    | ☆    | ↓    | ☆
| Gomi T, et al. [13]    | FCT | %ΔSI  | ←    | ←    | ←    |

FMX=ferumoxides, FCT=ferucarbotran, SNR=signal-to-noise ratio, Δ= difference between pre-SPIO and post-SPIO images, ※ statistically not significant, ☆ statistic evaluation not available

**Fig. 1:** Details of the previous reports dealing with the signal intensity change of the spleen before and after SPIO.
**Fig. 2:** Presumed mechanism of T2* and T2 value change before and after SPIO in normal and cirrhotic spleen. According to our data, splenic uptake of SPIO, which is most clearly shown as #T2, is elevated in patients with impaired liver function. Post-SPIO T2* and T2 are thus reduced in patients with impaired liver function. Pre-SPIO T2* and T2 of the spleen, however, may be determined by multiple factors including presence of congestion or Gamna-Gandy bodies, and therefore are inconsistent.
References

5. Gossuin Y, et al. MRI, 2005;23:1001-04,

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