Pancreatic exocrine function can predict cardiac iron in patients with iron overload and thalassemia

Poster No.: C-1540
Congress: ECR 2011
Type: Scientific Paper
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Keywords: Abdomen, Pancreas, Haematologic, MR, MR-Functional imaging, Laboratory tests, Diagnostic procedure, Blood, Haematologic diseases
DOI: 10.1594/ecr2011/C-1540

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Purpose

A significant but loose correlation was found between cardiac and pancreatic T2* relaxation times (2), however, in thalassemia patients with impaired function the association with endocrine function tests is spoiled by fatty infiltration of the pancreas. A decreased pancreatic exocrine function with subnormal serum amylase and lipase levels was found to be associated with pancreatic MRI signal-to-fat ratio in TM patients (3).

The purpose of this study was to measure R2* relaxation rates in the septum by MRI in comparison with the exocrine pancreatic function by means of serum pancreatic enzyme determination in patients with β-thalassemia.
Methods and Materials

All patients gave their written informed consent.

27 transfusion dependent TM patients (age 11 - 47 years, 9 females), had measurements of heart iron by ECG gated single breathhold multi-echo MRI-R2*, liver iron by biosusceptometry and pancreatic exocrine function by serum amylase (PAM) and lipase (LIP).

17 other patients with iron overload due to blood transfusion and iron loading (MDS, AML, SCD, DBA, CDA: n = 12, and HFE-associated hereditary hemochromatosis, non-transfused thalassemia intermedia: n = 5, respectively) were also investigated. Most patients (91%) were on long-term chelation or phlebotomy treatment. The selection of patients for cardiac MRI was based on elevated LIC with actual LIC > 700 µg/g liver (about 4.2 mg/g dry wgt) for 90% of patients.

Heart iron was assessed as transverse relaxation rate R2* by a mono-exponential fit to the averaged signal amplitudes in the septum with constant signal level offset (TE = 1.3 - 25.5 ms, #t = 2.8 ms, TR = 244 ms, FA = 20°) (Fig. 1). In-vivo liver iron concentration (LIC) was measured by SQUID biomagnetic liver susceptibility as described elsewhere (4).

Pancreatic serum amylase and lipase were measured in blood samples taken at the day of blood transfusion with a detection threshold of < 13 U/L (i.e. 12.9; normal range: 13 - 53 and 13 - 60 U/L, respectively).
**Figure 1:** Short Axis View of the Heart: The R2* is measured within the septum.

**Fig. 0:** Figure 1: Short Axis View of the Heart: The R2* is measured within the septum

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Results

The relationship between cardiac $R_2^*$ and pancreatic lipase for patients with β-thalassemia major (LIC = 597 - 9454 µg/g liver) and other patients with iron overload (LIC = 200 - 7681 µg/g liver) is shown in Fig. 2. For receiver operated characteristic (ROC) analysis, patients were divided in two groups (Fig. 3) with cardiac $R_2^*$ < 50 s$^{-1}$ or $T_2^*$ > 20 ms (range 23 - 49 s$^{-1}$) and $R_2^*$ > 50 s$^{-1}$ (range 51 - 387 s$^{-1}$) (see Table 1).

There was a highly significant correlation between LIP and PAM (spearman rank correlation $R_S = 0.70$, $p < 10^{-4}$). Lipase significantly correlated with $R_2^*$ ($R_S = -0.45$, $p = 0.0023$), while amylase only showed a negative trend ($R_S = -0.29$, $p = 0.057$). No significant correlation ($p > 0.2$) was observed with any other parameter (age, LIC, ferritin).

ROC analysis for correctly classifying patients with and without cardiac iron by pancreatic amylase revealed a significant discriminatory power (ROC curve area = 0.80, $p < 10^{-4}$) and equal true positive (sensitivity) and negative (specificity) rates of 75% at a cut-off level of 19 U/L.

An even better discrimination was found for the pancreatic LIP (ROC curve area = 0.88, $p < 10^{-4}$, sensitivity = specificity = 82% at a cut-off level of 18 U/L). A similar discrimination was achieved in patients with thalassemia major (ROC curve area = 0.89). In contrast, LIC could not predict cardiac iron (ROC curve area = 0.60, $p = 0.13$).

In Figure 2, the one misclassified hemochromatosis patient with LIP < 13 U/L and $R_2^*$ = 40 s$^{-1}$ had also an PAM level < 13 U/L and distinct cardiac siderosis in hypertrophic myocytes had been demonstrated by myocardial biopsy in the past. On the other hand, the 3 patients with $R_2^*$ > 50 s$^{-1}$ but LIP > 19 U/L, had PAM levels < 23 U/L. With the addition of pancreatic amylase in patients with LIP # 19 U/L, cardiac iron ($R_2^*$ > 50 s$^{-1}$) could be predicted to 67% also in these patients at a cut-off level of PAM < 23 U/L (ROC curve area = 0.83, $p < 10^{-3}$).
Fig. 2: Relationship between cardiac mid-papillary septal $R2^*$ (upper normal $R2^* < 50$ s$^{-1}$ or $T2^* > 20$ ms) and pancreatic serum lipase (lower normal cut-off level < 19 U/L) in 27 transfusion dependent β-thalassemia major patients (solid circles) and in 17 patients with iron overload due to blood transfusion or iron loading diseases (open squares).

Fig. 0: Fig. 2: Relationship between cardiac mid-papillary septal $R2^*$ (upper normal $R2^* < 50$ s$^{-1}$ or $T2^* > 20$ ms) and pancreatic serum lipase (lower normal cut-off level < 19 U/L) in 27 transfusion dependent b-thalassemia major patients (solid circles) and in 17 patients with iron overload due to blood transfusion or iron loading diseases (open squares).

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Figure 3: The Patients are divided in two groups: One with and the other Without cardiac iron measured with R2*.

For ROC analysis, patients divided in 2 groups

- cardiac R2* < 50 s⁻¹ or T2* > 20 ms (range 23 – 49 s⁻¹) = no iron
- cardiac R2* > 50 s⁻¹ or T2* < 20 ms (range 51 – 387 s⁻¹) = iron

Fig. 0: Figure 3: The Patients are divided in two groups: One with and the other Without cardiac iron measured with R2*.

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### Table 1.
Characteristics of patients with cardiac $R^*_2 < 50 \text{ s}^{-1}$ ($T2^*_c > 20 \text{ ms}$) and $R^*_2 > 50 \text{ s}^{-1}$: median values (range) and significance of differences (Wilcoxon-Mann-Whitney U-test) between patient groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$R^*_2 &lt; 50 \text{ s}^{-1}$</th>
<th>$R^*_2 &gt; 50 \text{ s}^{-1}$</th>
<th>p (U-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>28</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Diabetes (m/n)</td>
<td>3 / 28</td>
<td>8 / 16</td>
<td>0.009 *</td>
</tr>
<tr>
<td>Splenectomy (m/n)</td>
<td>6 / 28</td>
<td>6 / 16</td>
<td>0.3 *</td>
</tr>
<tr>
<td>Age (y)</td>
<td>28.5 (0-67)</td>
<td>33.3 (14-79)</td>
<td>0.25</td>
</tr>
<tr>
<td>LIC ($\mu g/g_{total}$)</td>
<td>2191 (300-9454)</td>
<td>3960 (883-8293)</td>
<td>0.25</td>
</tr>
<tr>
<td>Femtin ($\mu g/l$)</td>
<td>2195 (63-10529)</td>
<td>4484 (456-16391)</td>
<td>0.10</td>
</tr>
<tr>
<td>Amylase (U/L)</td>
<td>26.4 (12.9-51.0)</td>
<td>16.8 (12.9-32.9)</td>
<td>0.0011</td>
</tr>
<tr>
<td>Lipase (U/L)</td>
<td>32.6 (12.9-64.0)</td>
<td>16.3 (12.9-31.0)</td>
<td>&lt; 10.4</td>
</tr>
</tbody>
</table>

* 2-tailed Fisher exact test

**Fig. 0:** Table 1. Characteristics of patients with cardiac $R^*_2 < 50 \text{ s}^{-1}$ ($T2^*_c > 20 \text{ ms}$) and $R^*_2 > 50 \text{ s}^{-1}$: median values (range) and significance of differences (Wilcoxon-Mann-Whitney U-test) between patient groups.

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Conclusion

Adding to the suggestion that pancreatic R2* measurements could predict cardiac iron deposition (2), the exocrine pancreatic function might become an equivalent predictor, especially, as pancreatic iron seems to be found predominantly in the exocrine tissue.

A significant correlation was observed between pancreatic lipase and cardiac R2*, but not for liver iron, and ROC analysis for detecting patients with elevated cardiac R2* levels resulted in a high discrimination power by lipase. Using the exocrine pancreatic function parameters, serum pancreatic amylase and lipase, one could identify patients with iron overload in the liver also at risk of elevated cardiac iron concentration. However, this approach has to be verified on a larger patient scale. In any case, thalassemia patients and other iron overloaded patients with subnormal pancreatic amylase or lipase levels should undergo cardiac iron assessment by MRI. (see also Fig. 5 for suggestion)
Suggestion/ Hypothesis

- Lipase < 19 U/L
- Lipase ≥ 19 U/L
- Amylase < 23 U/L

Cardiac Iron?
(R2* > 50 s⁻¹)

Fig. 0: Suggestion/ Hypothesis

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References


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