Increased epicardial fat and signs of impaired sistolic left ventricular function in NAFLD Patients: MRI evaluation and correlation with abdominal fat.

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Purpose

NAFLD (Non Alcoholic Fatty Liver Disease) is the most prevalent cause of hepatic disease in Western Countries (1). It includes a wide spectrum of pathological syndromes, progressively more severe, ranging from steatosis to inflammation (s.c. NASH, Non Alcoholic Steatohepatitis) to fibrosis and it could lead to cirrhosis with the development of nodules of regeneration and Hepatocellular Carcinoma (HCC). NAFLD pathogenesis is complex and increased insulin-resistance plays a "key role" in it: it follows a frequent association and overlapping with other diseases such as diabetes and metabolic syndrome. In literature, many studies already explored correlation between NAFLD and cardiovascular disease (2); we found great variability in selection criteria and NAFLD diagnosis due to the simultaneous presence in examined patients of diabetes, hypertension or metabolic syndrome, well-known cardiovascular disease related illnesses. Furthermore, few of these studies searched for pre-clinical alterations and most of them used only one imaging technique, more often echocardiography. Visceral fat and epicardial fat have common embryogenetic elements and could be involved in the pathogenesis of NAFLD (3). Purpose of our study was to evaluate if there is an increased epicardial fat and if there are significant signs of systolic and diastolic dysfunction in patients with hepatic biopsy proven NAFLD.

Methods and Materials

A prospective single-centre case-control study was performed in our Magnetic Resonance (MRI) Service in collaboration with University Departments of Gastroenterology and Cardiology. Between October 2014 and February 2016, 33 patients with biopsy proven NAFLD (26 men, average age 46 years) and 13 healthy controls (7 men, average age 38 years) were enrolled. To exclude the presence of diabetes, metabolic syndrome and hypertension all patients underwent metabolic analysis. We assessed cardiac function and epicardial fat with transthoracic echocardiography (TTE) and MRI. MRI was performed, ECG synchronized, with Achieva 1.5 T MR System (Philips) and 32-channel coil. For every patient we acquired Steady State Free Precession (SSFP) axial sequences of the chest and short axis to cover both ventricles evaluating 30 phases of cardiac cycle to study volumes and function. Overall duration of the exam was averagely about 20 minutes. 14 out of 33 patients underwent also a basal abdominal MRI study with 3D Gradient Echo T1-weighted volumetric sequence for the quantification of visceral fat tissue. We calculated: volume of epicardial and visceral fat, left ventricle function parameters (cardiac output, ejection fraction, end-systolic and end-diastolic volume and systolic and diastolic speed of peak ejection). Axial SSFP sequences with OsiriX software (Pixmeo) were used to quantify epicardial fat by manually delimiting a region of interest (ROI) on epicardial fat and using an interpolation and computation function of the overall volume provided by the software (Figure 1). As for the epicardial fat, we evaluated visceral fat defining ROIs on the internal side of abdominal muscular or bony structures and selecting fat tissue signal intensity threshold values so we could be able to exclude vascular or visceral structures (parenchymatous or not) from volumetric computing (Fig. 2). With TTE, we calculated cardiac function parameters and epicardial fat thickness in the subcostal and long axis projections. Considering the limited sample size and the type of variables examined, the statistical analysis used non-parametric tests, such as the Mann-Whitney and the linear correlation coefficient Pearson test.

Images for this section:

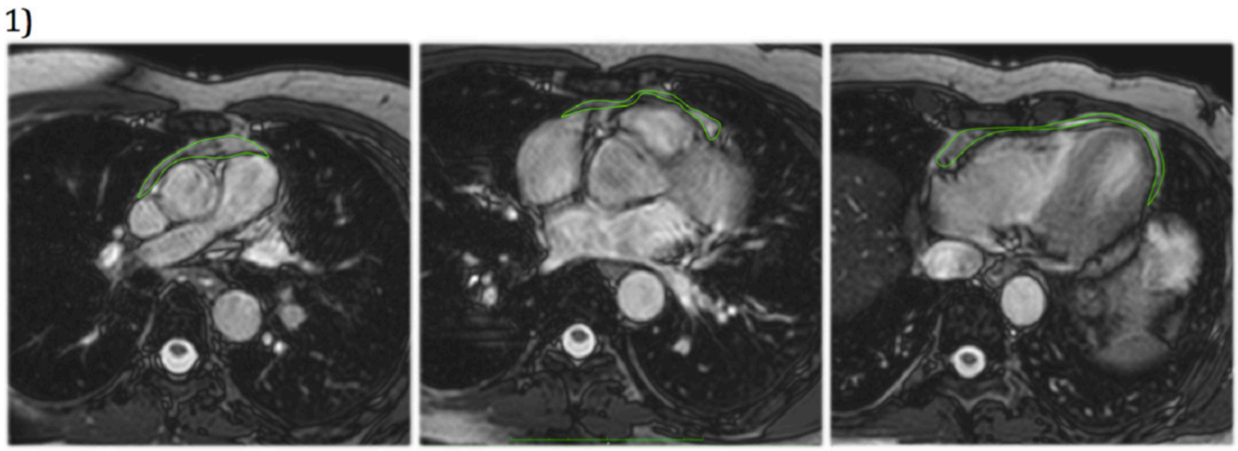

Fig. 1 SSFP axial images: heart sections at different levels. On every image, we selected a ROI following pericardial and myocardial profile to delimit epicardial fat tissue (hyperintense).

Fig. 1: SSFP axial images

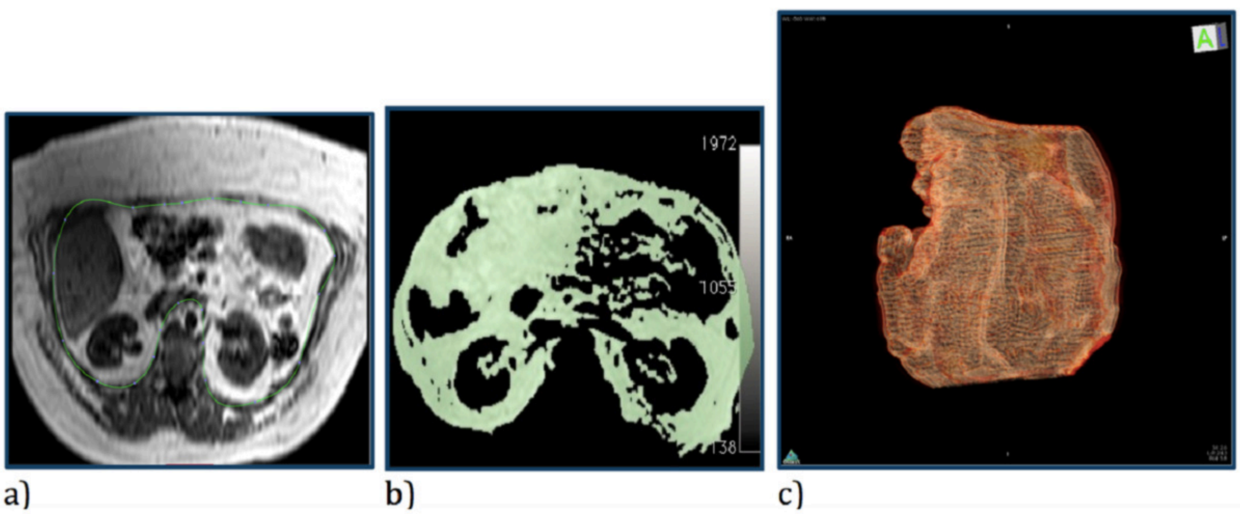

Fig. 2 a) GRE T1-weighetd abdominal sequence. We traced a ROI to delimit abdominal visceral cavity and fat tissue in it. **b)** Selecting "threshold" values, we are able to exclude from computation of visceral fat volume bowel loops and main abdominal vessels. **c)** "Selected" abdominal fat volume rendering at the end of the computation.

Fig. 2: GRE T1-weighted abdominal sequence.

Results

The analysis of glucose metabolism and anthropometric parameters showed a relevant difference of body mass index (BMI) between NAFLD patients and control group (BMI NAFLD patients: 27 kg/m2 vs 22 kg/m2); a difference in insulin sensibility and resistance indexes was also found (HOMA index NAFLD patients: 2,82 ± 1,7 vs 1,43 ± 0,5; p= 0,034. OGIS index NAFLD patients: 11,04 ± 1,6 vs13,1 ± 1,1; p= 0,004). In patients' group the volume of epicardial fat tissue measured with MRI was increased if compared with the control group (185±109 vs 52±30 cm3; p<0.0001), as well as its thickness measured with TTE (6.2±2.5 vs 2.8±3.5 mm; p=0.001). A direct positive correlation between epicardial and visceral adipose tissue was found in the subgroup of patients (n=13) who underwent the abdominal examination with MRI (r= 0.58; p = 0.03). Left ventricular ejection fraction was not statistically different between the groups, in both TTE and MRI evaluation ((52,3 ± 5,9 vs 55,2 ± 7,6; p= 0,36). In NAFLD patients' group, TTE showed an increased end-systolic left ventricular diameter (30±4 vs 27±4 mm; p=0.015), even though MRI did not point out a significant difference in end-systolic volume between the two groups (75.4±29.8 vs 80.5±31.6 ml; p=0.81). TTE showed that E/A ratio, a diastolic dysfunction parameter, is reduced in NAFLD patients (1.2±0.3 vs 1.5±0.4; p=0.03). The 1st/2nd filling volume ratio measured with MRI using volume/time curves analysis was significantly reduced in NAFLD patients (1.6±1.5 vs 3.1±1.8; p=0.04).

Conclusion

Many publications already investigated the quantification of epicardial adipose tissue volume using imaging modalities such as CT and MRI (4; 5). Our approach allowed us to estimate volume in a fast and reproducible way, with some sporadic difficulties, in particular in the delimitation of sovra-diafragmatic fat in patients who had an epicardial adipose tissue of limited thickness. The evaluation took 8-10 minutes per patient, in average. Furthermore, we used a sequence (axial SSFP) normally part of cardiac MRI protocols we use in our Institution.

Even though we need further evaluation to validate the statistical relevance of our results, TTE showed an increase of end-systolic diameter in NAFLD patients, albeit ejection fraction was not reduced. This finding could be referred to a preclinical systolic dysfunction, but MRI data analysis has not confirmed this result, in particular in the evaluation of end-systolic volume.

With TTE, trans-mitralic diastolic flow velocity can be measured in order to assess E/A ratio, which represents a widely used parameter for the evaluation of diastolic function (E= first filling velocity, which is faster and occurs during the valve opening; A= second filling velocity, which occurs during atrial systole). The role of MRI in the evaluation of diastolic function is still object of study. The first and more "intuitive" attempt was to analyze volume/time curves, but this approach has some limits, as reported by some Authors (6; 7) (Fig. 3). In our experience, analyzing time/volume curves we found that the 1st/2nd filling volume ratio was relevantly different between the two examined groups. MRI examination showed an increase in NAFLD patients in both visceral and pericardial fat tissue volume and the latter finding was confirmed by the increased thickness of pericardial fat measured with TTE. While TTE showed signs of preclinical systolic and diastolic dysfunction, MRI confirmed the presence of signs of diastolic dysfunction only, by now.

Positive correlation between the volume of visceral and epicardial fat is probably linked to their common embryological origin. Considering the pathogenesis of myocardial damage, the paracrine action of vasoactive and metabolic regulating factors released by epicardial adipocytes may influence, at least partially, the development of preclinical alterations of systolic and diastolic left ventricular function, since NAFLD patients have a more abundant epicardial fat.

Images for this section:

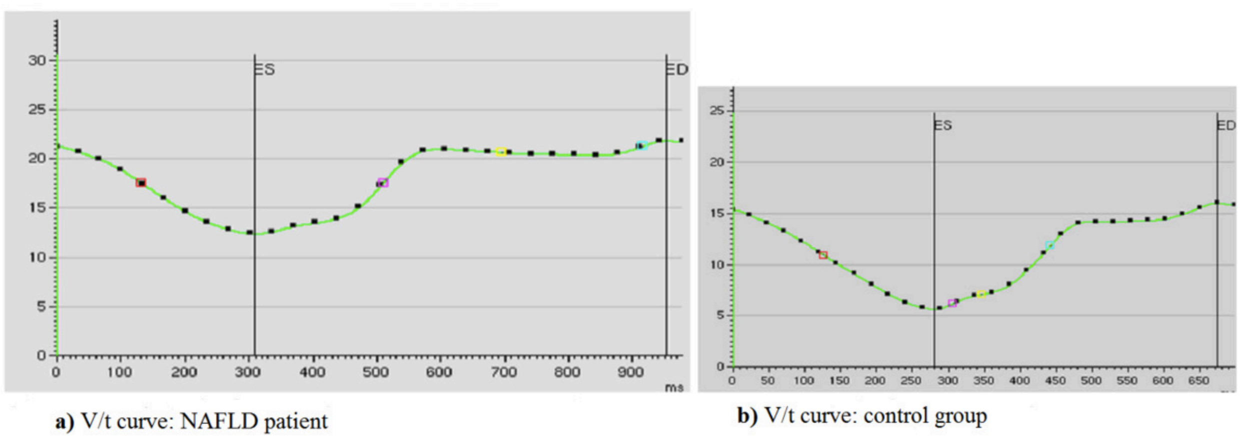

Fig. 3 "Ascending" part of the curve after end-systole time (ES) corresponds to diastolic filling phase. In diastolic dysfunction, we expect a "deceleration" of filling and, therefore, a lower slope of the curve (as shown in box **a**). Cardiac analysis software evaluates time and velocity of first filling (it occurs during mitral valve opening and corresponds to first part of the curve after ES) and second filling (it is due to atrial systole and corresponds to second part of the curve after ES).

Fig. 3: V/t curve analysis.

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