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Non-invasive assessment of hepatic steatosis and fibrosis and echocardiographic parameters of the function of the right ventricle

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Abstract: The gold standard for assessing liver fibrosis is core needle biopsy. Its invasive nature, however, limits its wide use. Hence the need for non-invasive methods in patients with hepar venostaticum due to right ventricular [RV] failure: one of them is the FIB4 index. Another method, Fibroscan, is based on an ultrasound technique from elastography.
Objective: to assess the correlation and determination indices between the FIB4 index and the assessment of liver stiffness by Fibroscan (E) on one hand and echocardiographic parameters describing RV function on the other hand.
The study group: 33 patients (74 ± 13 years) with heart failure due to pulmonary hypertension, arterial hypertension, valvular diseases, myocardial infarction or cardiomyopathy.
Results: echocardiography — RV dimension 38 ± 8 mm, systolic pressure in pulmonary artery (SPAP) 53 ± 24 mmHg, tricuspid annular plane systolic excursion (TAPSE) 17 ± 4mm, acceleration time of flow through the pulmonary valve (ACT) 79 ± 23 ms, the degree of tricuspid valve regurgitation 2 ± 1; the FIB4 result in this group — 2.54 ± 1.19, and the stiffness index E: 13.79 ± 12.55 kPa. Only RV dimension and the degree of tricuspid valve regurgitation showed moderately strong positive correlation with the stiffness index E: the correlation index — 0.327 and 0.382, respectively, with the determination index 27.9% and 43.4%, respectively.
Conclusion: The results emphasize the relationship between the morphological remodeling of the RV and the degree of secondary tricuspid regurgitation and the advancement of fibrotic changes in the liver and encourage the continuation of studies on larger groups of patients with a homogeneous etiology of RV failure, using a wider spectrum of echocardiographic parameters.

Keywords: right ventricular function, fatty liver disease, liver fibrosis.

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Introduction

The European guidelines for the prevention of cardiovascular diseases from 2021 list non-alcoholic fatty liver disease among comorbidities that may increase the risk of myocardial infarction and stroke or worsen the prognosis in a person with diagnosed cardiovascular disease [1]. Due to the frequent occurrence of conditions such as obesity, carbohydrate and lipid metabolism disorders or hypertension in people with this disease, a new nomenclature has been proposed for it and currently a distinction is made between: fatty liver disease associated with metabolic disorders (MASLD) for people who do not consume alcohol, fatty liver disease of mixed (metabolic-alcoholic) etiology (MetASLD) for weekly alcohol consumption between 140–350 g and 210–420 g for women and men, respectively, and alcoholic fatty liver for weekly alcohol consumption above 350 and 420 g depending on gender [2]. Epidemiological data show that the normal condition of the liver parenchyma occurs in 70% of the human population. In 25% there are grounds for diagnosing fatty liver disease, in the case of 3–5%, the steatosis is accompanied by an inflammatory process leading to steatohepatis, which results in 1–2% of people developing advanced fibrosis typical of liver cirrhosis [3]. The transformation from fatty liver disease to steatohepatitis and then to liver cirrhosis is a long-term process that can be rapidly accelerated by the coexistence of hypertension, and even more so by the presence of diabetes.

In Europe the importance of fatty liver diseases and their significance for cardiovascular risk is not sufficiently appreciated. Hence the initiatives of cardiologists under the acronyms FOIE GRAS and mtFOIE GRAS, the former aimed at improving the recognition, treatment and identification of risk factors for this disease among cardiac patients and the latter aimed at basic research to explain the molecular basis of the relationship between fatty liver and atherosclerosis [4]. Liver fibrosis (LF), which is the final stage of the process initiated by steatosis, is a factor associated with increased mortality in patients with heart failure [5]. At an earlier stage of knowledge, right ventricular [RV] failure was associated with liver changes of the hepar venostaticum type. Recently, a relationship has been suggested between the degree of LF and the degree of RV dysfunction [6]. For many years, the "gold standard" in diagnosing fatty liver disease and fibrosis was core needle biopsy, but due to its invasive nature and high risk of adverse events associated with the procedure, the test is not suitable for mass use. Currently, non-invasive tests based on ultrasound techniques are sufficient to assess the stage of fatty liver disease and fibrosis, among which the most widely used in practice is dynamic impulse elastography (transient elastography — TE) [7, 8]. On the other hand, the FIB-4 index, calculated on the basis of age and simple blood tests, can be considered a screening method. The first objective of this study was to assess the frequency of abnormal results of the assessment of liver parenchyma using the dynamic elastography technique (steatosis — CAP and fibrosis — E) in a group of patients of a family doctor's clinic who were consulted by a cardiologist. The next objective was to assess the correlation coefficient and the determination coefficient between the echocardiographic parameters assessing the RV function and the value of the parameters assessing LF on the basis of the measurement of liver stiffness — by means of dynamic elastography, as well as the correlation of this parameter with the value of the assessment of LF based on the FIB-4 index. The study was retrospective. The study group consisted of 33 outpatients with heart failure in the NYHA class I to IV. The mean age (± SD) was 74 years (± 13), women constituted a fraction of 0.55 of the study group. Among the study patients there were no cases of infectious, autoimmune, storage, and toxic backgrounds of liver disease. The etiology of heart failure was as follows: 12 patients (fraction 0.37 of the examined patients) had heart failure as a result of pulmonary hypertension,

7 patients (0.21) developed heart failure in the course of arterial hypertension, 7 (0.21) — in the course of valvular heart disease, 4 patients (0.12) — after a myocardial infarction, and 3 (0.09) in the course of cardiomyopathy. In the examined group, the mean ± SD BMI was 26.28 ± 4.28, there were 8 people with obesity I° — 5 among women and 3 among men. The inclusion criterion was giving consent to being included in the study as well as having an assessment of the liver by means of the dynamic impulse elastography method with the Fibroscan device and having a current echocardiographic examination from a cardiology clinic — both of these examinations were performed within a period of no longer than 6 months between them.

Methodology

The FIB-4 index calculator is a simple tool for estimating LF, and its simplicity allows it to be used on a wide scale also in primary care, because it only requires knowledge of the patient's age, alanine aminotransferase (ALT) activity and aspartate aminotransferase (AST) activity, as well as the platelet count from a blood count (PLT). The formula for calculating the FIB-4 index is this: age ([years] × AST [U/L]) / ((PLT [10^9/L]) × (ALT [U/L])^{½}). The calculator is a tool generally available on the web, e.g. https://fib4.pl/. The FIB-4 index value for people without LF is a result below 1.3. An abnormal value is understood as a value above 2.67, and the results between these values are the so-called "gray zone." High agreement between the estimation of LF based on the FIB-4 index and the results of histopathological examinations, in which fibrosis was assessed on a 4-point scale, was verified in the study by Sterling *et al.* [9, 10]

The non-invasive test for liver steatosis and fibrosis used in this study was the dynamic pulse elastography by means of the Fibroscan device, France. This method consists in sending an ultrasound wave through the device head and then assessing the return wave, on the basis of which the level of wave attenuation and the stiffness of the liver tissue are assessed. In this method, liver steatosis is assessed by means of the attenuation phenomenon, and the result is given as CAP — (controlled attenuation parameter) in decibels (dB/m). A result from 238 to 260 dB/m means steatosis from 11 to 33% of the liver parenchyma (S1), 261–290 dB/m — steatosis from 34 to 66% (S2), and from 291–400 dB/m — steatosis of more than 67% of the liver tissue (S3). Liver stiffness reflecting fibrosis is assessed in kilopascals (kPa) — a normal result should be between 2.5 and 5 kPa, a result <8 kPa indicates a low risk of LF, a result of 8–12 kPa intermediate risk, and a result above 12 kPa high risk of LF.

The parameters describing the RV function were obtained from echocardiographic examinations provided by patients from the cardiology clinic. Five parameters were used for the analysis: the first one is the RV dimension in the parasternal projection, which should not normally exceed 35 mm in healthy individuals. The next ones are: systolic pressure in the pulmonary artery (SPAP), which should not exceed 25 mmHg; the tricuspid annular plane systolic excursion (TAPSE), the normal value of which is above 17 mm; the acceleration time of flow through the pulmonary valve (AcT), which is normally above 105 ms, and the degree of regurgitation through the tricuspid valve, which was numerically defined as degree I, II, III or IV [11].

Statistics

For variables with a normal distribution, the mean and standard deviation (SD) were calculated, for variables with a discrete distribution — median and interquartile range (median[25; 75]). Using Excel MS Office 2023 software, correlation coefficients and determination coefficients were calculated.

The strength of correlation was assessed according to J. Guilford's classification: |r| = 0 — no correlation; 0.0< |r| ≤0.1 — slight correlation; 0.1< |r| ≤0.3 — weak correlation; 0.3< |r| ≤0.5 — average correlation; 0.5< |r| ≤0.7 — high correlation; 0.7< |r| ≤0.9 — very high correlation; 0.9< |r| <1.0 — almost complete correlation and |r| = 1 — complete correlation [12].

Results

Assessing the FIB-4 index in patients with cardiac diagnoses — we found that in 3 people it had a value not indicating LF, in 17 (fraction 0.52) the result was in the so-called "gray zone," while in 13 people (fraction 0.39) this screening test indicated a high risk of LF and the need for deeper hepatological diagnostics.

As far as the CAP assessment was concerned, in 24 patients out of the 33 the Fibroscan device did not detect any signs of fatty liver disease (fraction 0.72), in 2 (0.06) the first degree of fatty liver disease (S1) was diagnosed, in 4 (0.12) — the second degree of fatty liver disease (S2) and in 3 (0.09) — the third degree of fatty liver disease (S3), according to the classification given in the methodology. The minimum value of the CAP parameter was 156 dB/m, the maximum 336 dB/m, mean ± SD — 22.57 ± 46.0 dB/m.

In terms of the second parameter — E reflecting LF — in 15 people (fraction 0.45) the risk of fibrosis of this organ was estimated as low, and in 5 and 13 as moderate and high, respectively (total fraction 0.55 of the study group). The minimum value of the E index was 3.7 kPa, the maximum — 67.9 kPa, and the median [25; 75] — 10.2 [5.4; 18.5] kPa.

There was a weak correlation between the values of the FIB-4 index and the values of the E measurement (r = 0.23) with the determination coefficient R2 = 0.05.

Table 1 presents the results of 5 selected parameters of the assessment of the right heart ventricle and the value of the fraction of patients whose result was abnormal.

The numerical data presented in Table 2 show that an average correlation was observed between the RV dimension and the LF index E with the value of r = 0.327 and for the degree of tricuspid valve regurgitation and E with the value of r = 0.382 with the determination coefficients of 0.279 and 0.434, respectively. The remaining correlations from Table 2 were of a weak nature according to Guilford's classification.

Table 1. Results of echocardiographic assessment of the right ventricle of the heart.

Parameter [abbreviation — unit — value in healthy individuals]	Mean ± SD	Fraction of people with abnormal result
Right ventricle dimension [mm — <35]	38.46 ± 8.11	0.73
Systolic pulmonary artery pressure — [SPAP — mmHg — <25]	53.48 ± 24.48	0.97
Tricuspid annular plane systolic excursion [TAPSE — mm — >17]	17.28 ± 4.3	0.64
Pulmonary valve flow acceleration time [AcT — ms — >105]	79.37 ± 23.27	0.79
Degree of tricuspid valve regurgitation [degree — from I to IV]	2.25 ± 1.13	0.94

Table 2. Correlation coefficient and coefficient of determination for liver fibrosis and right ventricular echocardiography parameters.

Parameter [abbreviation]	Correlation co-efficient [r]		Determination co-efficient [R^2]	
	Assessment of liver fibrosis by means of FIB-4	Assessment of liver fibrosis using Fibroscan — E	Assessment of liver fibrosis by means of FIB-4	Assessment of liver fibrosis using Fibroscan — E
Right ventricle dimension	0.236	0.327	0.28	0.279
Systolic pulmonary artery pressure [SPAP]	–0.054	–0.141	0.012	0.104
Tricuspid annular plane systolic excursion [TAPSE]	–0.244	–0.219	0.046	0.308
Pulmonary valve flow acceleration time [AcT]	–0.256	–0.138	0.012	0.049
Degree of tricuspid valve regurgitation	0.146	0.382	0.003	0.434

Discussion

The most important result of our study is the possibility of non-invasive detection of alarming changes in the liver parenchyma in cardiac patients: in almost every 5th patient, the result of the dynamic pulse elastography test indicated fatty liver disease, and in more than half of them, tissue features typical of fibrosis were noted.

When the FIB-4 index was used, the percentage of people whose result indicated a high risk of LF was lower than when the dynamic pulse elastography method was used, which means that the assessment of the risk of LF based on parameters derived from the FIB-4 index from a blood test is less effective than pulsed elastography. While fatty liver is a condition associated with modifiable cardiovascular risk factors, for which both pharmacological and non-pharmacological methods of treatment are available, in the case of fibrosis, until recently there was no specific pharmacotherapy for this condition. Great hopes are associated with the possibility of regression of LF through the use of drugs interfering with the incretin system, which not only reduce body weight, but which also have a beneficial effect on reducing blood pressure, carbohydrate and lipid metabolism [13]. The second important result of our study is the demonstration of an average correlation between simple parameters derived from echocardiographic assessment, i.e. RV dimension and the degree of tricuspid valve regurgitation and the risk of LF. This issue was already the subject of one earlier study — Chen *et al.* showed in their work on 131 patients with tricuspid regurgitation secondary to left heart valve disease that the effective area of the tricuspid valve outlet, right atrial pressure and the dimension of the inferior vena cava correlate most strongly with the so-called "liver stiffness," which reflected the severity of fibrosis [14]. One of the significant limitations of our study is the relatively small size of the study group, which did not allow for the full use of statistical methods to assess the significance of the identified relationships [15]. Another limitation is the heterogeneous etiology of heart failure; however, due to the pilot nature of our study, we decided to analyze the obtained results in patients with a wide spectrum of causes of heart failure.

Conclusions

Non-invasive assessment of fatty liver and detection of advanced changes may contribute to an intensification of treatment of modifiable cardiovascular risk factors in patients under the care of a cardiologist.

Our results emphasize the relationship between morphological remodeling of the right ventricle and the degree of secondary tricuspid regurgitation with the advancement of fibrotic liver changes and encourage further studies on a larger group of patients and separate analyses in subgroups with homogeneous etiology of RV failure using a wider spectrum of echocardiographic parameters illustrating the RV function.

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