

**“VICTOR BABEȘ” UNIVERSITY OF MEDICINE AND
PHARMACY TIMIȘOARA
FACULTY OF MEDICINE
5TH DEPARTMENT – INTERNAL MEDICINE I
PÂRVĂNESCU H. TUDOR**



SUMMARY OF PHD THESIS

**THE ROLE OF CONVENTIONAL AND
MODERN ECOCARDIOGRAPHY IN THE
ASSESSMENT OF THE LEFT HEART
FUNCTION IN PATIENTS WITH
METABOLIC SYNDROME**

Thesis Advisor

Prof. Dr. TOMESCU MIRELA CLEOPATRA

Timișoara

2021

TABLE OF CONTENTS

1.INTRODUCTION	2
2.Non-alcoholic Fatty Liver Disease Associated With Metabolic Syndrome, a Major Risk Factor for Atherosclerotic Disease.....	4
3. Association Between Subclinical Left Ventricular Myocardial Systolic Dysfunction Detected by Strain and Strain-Rate Imaging and Liver Steatosis and Fibrosis Detected by Elastography and Controlled Attenuation Parameter in Patients with Metabolic Syndrome.....	6
4.Significant Association Between Left Ventricular Diastolic Dysfunction, Left Atrial Performance and Liver Stiffness in Patients with Metabolic Syndrome and Non-Alcoholic Fatty Liver Disease.....	8
5. GENERAL CONCLUSIONS	10

1. INTRODUCTION

Metabolic syndrome (MS) is defined by the presence of 3 out of 5 of the following criteria: abdominal obesity (waist circumference > 102 cm in men or 88 cm in women), atherogenic dyslipidemia: serum triglycerides (TG) greater than 150 mg / dL or high serum lipoproteins density (HDL) less than 40 mg / dL (men) or less than 50 mg / dL (women), high blood pressure (BP) (BP > 130/85 mmHg) or insulin resistance with impaired fasting blood glucose.

MS is a disease characterized by the presence of several cardiovascular risk factors, such as high blood pressure, abdominal obesity, insulin resistance, hyperglycemia and dyslipidemia. It usually affects patients with obesity and sedentary lifestyle. About 25% of the adult population worldwide suffers from MS.

This condition is associated with an increased risk of diabetes, stroke and myocardial infarction. Some clinical studies have shown that MS is linked to atherosclerotic vascular disease and heart failure. Patients with MS often are diagnosed with liver diseases such as nonalcoholic fatty liver disease (NAFLD). Compared with patients without NAFLD (1% to 3%), patients with NAFLD have a significantly higher risk of cardiovascular events. This association can be explained by several mechanisms. Previous studies have shown that NAFLD is associated with myocardial insulin resistance and also predisposes to structural damage to the left ventricle and ultimately diastolic dysfunction.

NAFLD involves hepatic steatosis (a less dangerous disease without hepatocellular disease, liver inflammation or fibrosis) and nonalcoholic steatohepatitis (NASH). NASH is a more severe disease and is associated with the presence of hepatic steatosis, hepatocellular pathology and inflammation, with or without fibrosis. A recently published meta-analysis showed that 35% of patients with NASH develop cirrhosis of the liver in about 7 years. However, most patients with NASH died from cardiovascular disease rather than liver disease complications.

By using conventional echocardiography and tissue Doppler ultrasound, evidence of myocardial dysfunction was obtained. However, the sensitivity of conventional echocardiographic parameters to assess systolic cardiac function is low and early changes in myocardial contractility cannot be detected. In the last few years, two-dimensional speckle tracking echocardiography (STE-2D) has become a more reliable method of identifying subtle cardiac dysfunction by quantitatively evaluating myocardial malformations. The key element of speckle tracking

ultrasound is elongation, expressed as a percentage (%). The strain (strain) in each ventricular region can be evaluated and the average of these values can be obtained (LV contraction peak). This method can evaluate myocardial fibers according to their specific arrangement (longitudinal deformation of subendocardial fibers, circumferential and radial deformation of subepicardial fibers). There is a special relationship between left atrial function (LA) and left ventricular function (LV). During left ventricular systole, the LA may resemble a reservoir. At the beginning of ventricular diastole, LA is emptied by a suction effect, and at the end of LV diastole, LA will act as a pump. LA remodeling is associated with LV remodeling. A number of studies have shown that LA function has a prognostic effect on both cardiac and non-cardiac death.

2. Non-alcoholic Fatty Liver Disease Associated With Metabolic Syndrome, a Major Risk Factor for Atherosclerotic Disease

Non-alcoholic fatty liver disease (NAFLD) is a vast chapter of liver pathology in medical practice. Prevalence in the general population is approximately 10-30%, being higher in developed and current countries` development.

There is an association between NAFLD with insulin resistance and metabolic syndrome. A possible explanation of this association would be that the NAFLD patients often present abnormalities in carbohydrate metabolism, are overweight or obese, and hypertensive.

However, the clinical and epidemiological significance of a NAFLD is not fully elucidated. The fact that NAFLD is associated with traditional cardiovascular risk factors (hypertension, dyslipidemia, obesity, sedentary lifestyle, insulin resistance, endothelial dysfunction, and inflammation) placed patients with NAFLD in a risk category increased for cardiovascular events.

Patients with metabolic syndrome present, when compared to control subjects, a significantly higher left ventricular mass index, as well as an impairment in cardiac diastolic function. These are side effects of insulin resistance, obesity, hypertension . Unfortunately, only a few echocardiographic studies included subjects with NAFLD, but the results regarding left ventricular hypertrophy and diastolic dysfunction were similar to those found in the presence of the syndrome metabolic.

The finding of a subclinical (asymptomatic) cardiac dysfunction in patients with NAFLD is not surprising if we consider the fact that left ventricle hypertrophy and diastolic dysfunction are closely correlated with insulin resistance . Endothelial dysfunction is recognized as an early sign of atherosclerosis, both in diabetics and in non-diabetics. There is an independent association between the alteration of the vasodilation mediated flow and the presence of NAFLD. Endothelial dysfunction was more severe in those with NAFLD compared to those with simple hepatic steatosis, confirming the possibility of correlating cardiovascular risk with the severity of NAFLD.

To explain the causes of subclinical cardiac dysfunction in patients with NAFLD, the effects of hepatic steatosis on cardiac metabolism were evaluated. The more severe the hepatic steatosis, the more severe the systemic insulin resistance was found, and this was associated with a reduction in myocardial glucose uptake and extraction, with a decrease in coronary reserve function, and with increased plasma levels of inflammation markers and molecules of vascular adhesion.

In conclusion, the data published so far suggest that the patients with NAFLD have multiple cardiovascular risk factors and that in these patients, cardiovascular deaths are more common than those caused by the liver. NAFLD is associated with an increased risk of cardiovascular disease events in both diabetics and non-diabetics. So far, it is not known whether NAFLD amelioration could prevent or slow down the onset or worsening of atherosclerotic cardiovascular disease. The prognostic value of NAFLD in the stratification of cardiovascular risk is still controversial.

3. Association Between Subclinical Left Ventricular Myocardial Systolic Dysfunction Detected by Strain and Strain-Rate Imaging and Liver Steatosis and Fibrosis Detected by Elastography and Controlled Attenuation Parameter in Patients with Metabolic Syndrome.

The evidence of myocardial dysfunction in individuals with MS was gathered by studies using conventional and tissue Doppler echocardiography. Though conventional echocardiographic parameters for assessment of systolic cardiac function have a poor sensitivity and fail to detect subtle decreases in myocardial contractility.

Association between NAFLD, assessed by liver vibration-controlled transient elastography (VCTE) and by controlled attenuation parameter (CAP), and subtle abnormalities in LV function assessed by SI and SRI, was not yet studied. Therefore, we wanted to explore whether there is any association between hepatic steatosis and/or fibrosis and cardiac dysfunction in MS patients.

This prospective study was performed between January 2019 and January 2020 in the Department of Cardiology in Timisoara Emergency City Hospital Timisoara and the Department of Gastroenterology and Hepatology in Timisoara Emergency County Hospital. We enrolled adult subjects with MS and compared their demographic, clinical, biological, and echocardiographic characteristics with those of a control group, that included age- and sex- matched adult subjects without MS. All MS patients were evaluated by conventional mono (M) and two-dimensional (2D) echocardiography and by 2D-STE, as well as by VCTE, and by CAP.

MS patients had significantly more frequent diabetes mellitus and systemic hypertension, had higher weights, body mass indexes, and waist circumferences, higher values of fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c), and of triglycerides, but significantly lower values of total and high– density lipoprotein (HDL) cholesterol.

SI and SRI detected subtle LV systolic dysfunction in 47 (31%) MS patients, reflected by reduced LS and LSR. Compared with controls, MS patients had significantly impaired LS ($P < 0.0001$), and LSR ($P < 0.0001$). No significant differences were observed among MS and control patients regarding CS, CSR, RS and RSR.

In univariate regression analysis, the variables associated with reduced LS in MS patients were diabetes mellitus, waist circumference, age, and liver stiffness measurement, while factors associated with reduced LSR were diabetes, waist circumference and liver stiffness measurement.

In multivariate analysis, the factors independently associated with reduced LS were diabetes ($P<0.005$) and LSM ($P<0.0001$). Reduced LSR was also independently associated in multivariate analysis with diabetes ($P<0.02$) and with LSM ($P<0.001$).

LVEF was similar in the two groups ($P=0.05$), but the 2D-STE identified a significant difference in LS values between the case and control groups. 2D-STE was able to assess a subtle LV systolic dysfunction in 47 MS patients (46%) and in 12 controls (8%), $P<0.0001$. The risk for LV systolic dysfunction was 3 times higher in the hypertensive (OR=8.7; 95% CI: 5.1 to 14.8, $P<0.0001$) and 5.5 times higher in diabetic patients with MS (OR=18.3; 95% CI: 9.8 to 34.2, $P<0.0001$).

The risk for LV diastolic dysfunction was 3.6 times higher in MS with severe steatosis (OR=3.6; 95% CI: 1.9 to 6.8, $P<0.0001$) and 8 times higher in patients with severe fibrosis (OR=14.8; 95% CI: 8.7 to 25.1, $P<0.0001$). The risk for LV systolic dysfunction was double in MS with severe steatosis (OR=3.6; 95% CI: 1.9 to 6.8, $P<0.0001$) and 1.7 times higher in MS with severe fibrosis (OR=4.1; 95% CI: 2.1 to 7.7, $P<0.0001$).

Our study indicates that MS patients have a high prevalence of LV diastolic and systolic dysfunction. While diastolic heart dysfunction can be detected by conventional echocardiographic measurements, the assessment of subtle systolic dysfunction needs speckle tracking echocardiography. This finding recommends 2D-STE as a routine echocardiographic examination in MS patients, as revealing and early treatment of cardiac disorders are vital issues for better outcomes in these subjects. Cardiac dysfunction in MS patients was significantly and independently associated with severe hepatic fibrosis and steatosis, detected by transient VCTE and CAP.

Early assessing of both heart and liver disease in MS individuals is important, in order to initiate lifestyle changes and medical therapy, aimed to correct all cardiovascular risk factors, including abdominal obesity.

4. Significant Association Between Left Ventricular Diastolic Dysfunction, Left Atrial Performance and Liver Stiffness in Patients with Metabolic Syndrome and Non-Alcoholic Fatty Liver Disease

Probably almost 25% of the adult persons have MetS. Some clinical researches suggest that MetS is associated with the existence of vascular atherosclerosis and heart failure.⁵ The HF syndrome is like an iceberg, with a visible segment that includes the symptomatic HF patients, and a much bigger invisible ("below the waterline") segment that includes the asymptomatic patients.

In the present study, we meant to evaluate whether there is any correspondence between LV diastolic dysfunction and different degrees of liver steatosis and fibrosis in MetS subjects. We also wanted to see whether the LA performance could predict LV diastolic dysfunction and might be associated with the extent of NAFLD.

This observational study was achieved from January 2019 to January 2020 in the Department of Cardiology, and in the Department of Gastroenterology and Hepatology of the Victor Babes University of Medicine and Pharmacy, Timisoara.

We registered consecutive adult patients with MetS and a normal LVEF scheduled for a medical visit in the Cardiology Department that agreed to be evaluated by liver elastography. The control group consisted of adults with a normal LVEF and no MetS, selected to be sex- and age-matched with the enrolled MetS patients, and willing to participate in this study. The baseline characteristics were compared among the two groups. All subjects were assessed by VCTE, CAP as well as by two-dimensional (2D) conventional and speckle-tracking echocardiography (STE).

150 MetS subjects were enrolled in the research group and 150 age- and sex- corresponding subjects without MetS were included in the control group.

MetS patients were significantly more frequent hypertensive, diabetics, obese. They presented higher values of triglycerides, glycosylated hemoglobin (HbA1c), FPG, and lower values of total cholesterol and of high-density lipoprotein (HDL) cholesterol.

In univariate regression analysis, the variables associated with LV diastolic dysfunction in MetS patients were: liver steatosis grade ≥ 2 , liver fibrosis grade ≥ 2 , the longitudinal LA peak strain during the reservoir phase, the LA strain rate during ventricular contraction and the LA stiffness.

In multivariate logistic regression, two variables were selected as independent predictors of LV diastolic dysfunction, namely the liver stiffness ($P=0.0003$) and the LA stiffness ($P<0.0001$). The adjusted variable in multivariate analysis was the presence of the metabolic syndrome.

Accordingly, although in our study the LA diameters, volumes, and ejection fractions between the MetS subjects and the controls did not differ significantly, the 2D-STE measured LA deformation, evaluated by the peak LA strains and strain rates was significantly impaired in the presence of the MetS ($P<0.0001$).

In our study, analyzing the ROC curve of the LA stiffness predictive capacity for LV diastolic dysfunction in MetS subjects, we found that the cut-off value of 0.38 had a high specificity (96%) and a sensitivity of 45%, completing the echocardiographic requirements to avoid false- positive statements.³

In our study, the prevalence of LV diastolic dysfunction was 52% in the MetS patients and 39% in the control group. The higher prevalence of the LV diastolic dysfunction could be explained by the fact that 89% of the MetS patients had diabetes and 80% were hypertensive.

The present study confirmed the association between liver fibrosis ≥ 2 stiffness and left ventricular diastolic dysfunction in MetS patients. The MetS patients in our study had a 3 fold higher risk for having an increased LA_{sf} when compared to the control group ($P<0.001$). The increased LA_{sf} is another parameter indicating LV diastolic dysfunction. A LA_{sf} >0.38 was positively associated with a liver fibrosis stage $F\geq 2$ and a liver steatosis stage $S\geq 2$ ($P<0.0001$).

There were no significant differences between the two groups concerning the conventional parameters of LV structure and systolic function, but significantly more of the MetS patients presented LV diastolic dysfunction. We found no differences regarding the LA diameters, volumes and ejection fractions between the MetS patients and the controls.

By contrast, the 2D-STE identified subtle LA dysfunction in the MetS subjects, revealed by significant lower longitudinal strains and strain rates during the ventricular contraction, the ventricular early diastolic filling and the atrial contraction. LA stiffness was significantly higher in the MetS subjects ($P<0.0001$).

■ GENERAL CONCLUSIONS

The thesis presents a topical issue with many unknowns in medical practice, such as the metabolic syndrome associated with cardiovascular diseases in patients with or without liver disease.

The main feature of the MS is defined by the risks of cardiovascular disease and also the risk of developing diabetes.

Once detected, MS must have a multidisciplinary approach because of the multitude of its components, but also because of the occurrence of complications (those that require increased attention being those in the cardiovascular area).

Our publication indicates that patients with MS have a high prevalence of cardiac dysfunction. While diastolic cardiac dysfunction can be detected by conventional echocardiographic measurements, the evaluation of subtle systolic dysfunction requires speckle tracking echocardiography.

This finding recommends 2D STE as a routine echocardiographic examination in MS patients, because recognition and early treatment of the heart lesions are some of the most important issues for better outcomes in these subjects. Cardiac dysfunction in patients with MS has been significantly and independently associated with severe hepatic fibrosis and steatosis, detected by transient VCTE and CAP.

Early recognition of heart and liver disorders in subjects with MS is extremely important, because appropriate lifestyle changed and medical therapy could prevent or at least delay the onset of heart failure and cirrhosis of the liver.

These measures could reduce morbidity and mortality, as well as costs to cover health insurance.