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PhD THESIS

**MULTIDISCIPLINARY APPROACH TO PATIENTS WITH
METABOLIC SYNDROME AND ISCHEMIC STROKE**

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Key words : metabolic syndrome, cardiovascular risk, subclinical cardiovascular dysfunction, imagistic, ischemic stroke, acute coronary syndrome, prognosis

1. INTRODUCTION - MOTIVATION

Metabolic syndrome (MS) is defined by the presence of a variety of cardiovascular risk factors, including dyslipidemia, abdominal obesity, insulin resistance, and high blood pressure. It predominantly affects sedentary and obese adults and has been associated with an increased risk of developing stroke, heart failure, diabetes, myocardial infarction, and other cardiovascular diseases. The incidence of MS has increased in recent years, endangering the health of the general population. According to current estimates, MS affects about 25% of the adult population.

Stroke is a major source of morbidity and mortality worldwide, the second leading cause of death and the third leading cause of disability - adjusted life years (DALY), as shown in World Health Organization (WHO) report on global mortality and health. Stroke is often preceded by transient ischemic attacks (TIAs).

Approximately 20 to 30% of ischemic strokes have an unidentified etiology and are classified as cryptogenic. Using modern diagnostic procedures, up to 30% of cryptogenic strokes have been detected as having a cardioembolic etiology due to silent atrial fibrillation (AF).

Ischemic atherosclerotic strokes can be caused by a variety of different processes, including in situ thrombotic obstruction, artery-to-artery embolism, branch occlusion, and circulatory failure.

Stroke prevention involves the correct classification of the risk of the patient with metabolic syndrome and the early establishment of a healthy lifestyle and the therapeutic control of risk factors.

2. THE GENERAL PART

The ideal cardiovascular health would be defined by the presence of the following seven factors: (1) non-smoking condition or smoking cessation more than one year ago; (2) body mass index ≤ 25 kg / m²; (3) physical activity of at least 150 minutes (moderate intensity) or 75 minutes (vigorous intensity) each week; (4) 4-5 key components of a healthy diet in accordance with current guidelines of the American Heart Association; In addition, a total cholesterol level of less than 200 mg / dL, a blood pressure of less than 120/80 mm Hg and a fasting blood glucose of less than 100 mg / dL are required.

Neither in Europe nor in the United States is people's cardiovascular health even close to ideal. As the economies of many low- and middle-income countries expand, we may see even worse health outcomes in the future, with the incidence of high blood pressure, diabetes, obesity, smoking and reduced physical activity.

The better the general health of the subject, the better his cognitive function. A link between functional cognitive decline and cardiovascular health has recently been shown. The decrease in the Barthel Activities of Daily Living score, which coincided with a decrease in the number of ideal health variables, was defined as "vascular functional impairment."

Another example of a condition caused by a constellation of multiple cardiovascular risk factors is metabolic syndrome. It is defined by the combination of three or more of the following conditions: abdominal obesity (abdominal circumference ≥ 80 cm in women and ≥ 94 cm in men), fasting blood glucose ≥ 100 mg / dL or treatment for diabetes, increased triglycerides ≥ 150 mg / dL or treatment for hypertriglyceridemia, low HDL cholesterol $<40/50$ mg / dL in men / women; hypertension (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or treatment for high blood pressure).

3. THE SPECIAL PART

3.1. PURPOSE AND OBJECTIVES

When it comes to strokes, the phrase "accident" seems to be a misnomer, because there is nothing "accidental" about their occurrence; rather, it takes years of subclinical pathological conditions to develop into a stroke.

If we want to reduce the increasing prevalence of ischemic stroke, we need to focus on the proper management of cardiovascular risk factors.

Although the treatment of stroke is the responsibility of neurologists, its prevention requires a multidisciplinary approach, including cardiologists, internists, diabetologists, family doctors.

Subclinical pathological conditions develop when the risk factors are not well managed, whether it is the presence of small atheromatous plaques in the carotid arteries, subclinical changes in cardiac function that promote atrial fibrillation or early changes in brain structure. At some point, the subclinical pathological conditions will eventually reach the clinical threshold if the necessary measures are not taken.

Healthcare professionals may be involved in the process too late after the patient has suffered a stroke, transient ischemic attack, atrial fibrillation, or myocardial infarction.

Therefore, in my doctoral thesis I aimed to identify subclinical functional and structural changes in the heart and arteries of adults with metabolic syndrome, and evaluate their association with major cardiovascular events.

The doctoral research included three studies, which had as objectives:

1. To investigate whether patients with metabolic syndrome have subclinical cardiac dysfunction
2. To evaluate the role of subclinical dysfunction of the left atrium in identifying the cardioembolic etiology of transient ischemic attack in patients with asymptomatic paroxysmal atrial fibrillation
3. To determine if there is a significant association between the values of the peak circumferential strain and its velocity in the common carotid artery and the occurrence of major cardiovascular events in patients with metabolic syndrome.

3.2. MATERIAL AND METHODS

3.2.1. The first study was performed between January 2019 and January 2020, at the Timișoara County Hospital. It included 150 patients with metabolic syndrome and non-alcoholic fatty liver disease, who were compared with 150 adult subjects of the same age and sex, but without metabolic syndrome. Only asymptomatic subjects with no history of cardiovascular disease were enrolled. Data obtained by hepatic elastography, conventional echocardiography and those obtained by two-dimensional speckle-tracking of the heart were compared.

3.2.2. The second retrospective study included patients over the age of 50 who had a transient stroke (TIA) from November 2017 to 2021, who were in sinus rhythm at the time of TIA. All patients were evaluated by echocardiography 14 days after discharge for TIA, so as not to surprise AS in stunning after a possible episode of AF. Those in atrial fibrillation at the time of echocardiographic examination were excluded from the study.

3.2.3. In this prospective observational study we enrolled 220 adult patients with MS (60.7 ± 7.5 years, 53% men), asymptomatic and without a history of cardiovascular disease. Two-dimensional 2D-STE ultrasound of the common carotid arteries (ACC) was used to determine the peak circumferential strain (CS) and its velocity (CSR). Patients with MS were followed for a period of three years, recording all the major cardiovascular effects that occurred during this time.

3.3. Results

3.2.1. The age of the patients was 62 ± 10 years (31-85 years), 54% were men.

Conventional echocardiography found that adults with MS had a much more frequent subclinical left ventricular dysfunction (LV) of the diastolic type compared to the control group ($P < 0.0001$).

2D-STE echocardiography revealed subclinical dysfunction of the left atrium (AS), demonstrated by a reduction in longitudinal atrial strain and its velocity. Atrial dysfunction was also significantly more common in patients with MS ($P < 0.0001$).

The stiffness of the AS is the level of pressure in the AS needed to increase its volume to a certain level and correlates with the amount of fibrous tissue in the atrial wall. Atrial stiffness is calculated as the ratio of I / O value and AS tank strain value. Its accuracy is due to the fact that it derives from two variables determined by two different echocardiographic procedures. AS stiffness is a good indicator of LV filling pressure. In our analysis, an atrial stiffness value of > 0.38 was statistically significantly correlated with subclinical LV diastolic dysfunction, with a specificity of 96% and a sensitivity of 45%.

In the univariate analysis, diastolic LV dysfunction in MS patients was significantly associated with grade ≥ 2 hepatic steatosis, grade ≥ 2 liver fibrosis, reduced longitudinal strain of the AS, and AS stiffness.

In the multivariate analysis, two variables independently associated with LV diastolic dysfunction were identified, namely hepatic stiffness ($P = 0.0003$) and AS stiffness ($P < 0.0001$).

The association between AS stiffness and LV diastolic dysfunction in MS patients had a sensitivity of 45% and a specificity of 96%, the calculated cut-off value being > 0.38 .

3.2.2. The second study included 190 patients ≥ 50 years of age with sinus rhythm who had a TIA of unclear etiology. In 33% of them, the medical documents recorded episodes of paroxysmal atrial fibrillation (FAP). Patients were divided into 2 groups, depending on the presence (group I) or absence (group II) of FAP episodes.

Patients with TIA and episodes of FAP were older (mean age 67.5 vs. 60 years, $P < 0.0001$), female (48% vs. 32%, $P = 0.04$), with a history of stroke (65% vs. 23%, $P < 0.0001$) and a higher CHA2DS2-VASc score ($P < 0.01$).

Regarding the functional parameters of the SA, significant differences were found between the two groups. Those with FAP episodes had higher values of the indexed volume of the AS ($P < 0.001$), lower values of the emptying fraction of the AS ($P < 0.0001$), as well as altered patterns of deformation compared to the control group. I WOULD.

In the univariate analysis, the factors significantly associated with FAP were: age, female gender, the indexed volume of the AS and the emptying fraction of the AS, as well as the strainers of the AS.

The multivariable logistic regression analysis identified three parameters independently associated with FAP, namely: age, AS emptying fraction (LAEF), and AS tank function alien (LARVS).

Analysis of the ROC curves of these independent parameters revealed the following values for sensitivity and specificity: age (Area under curve AUC = 0.922, sensitivity: 72.92, specificity: 90.1, $P < 0.0001$), LARVS (AUC = 0.915, sensitivity: 100.0, specificity: 64.8, $P < 0.0001$), and LAEF (AUC = 0.717; sensitivity: 72.9; specificity: 90.1; $P < 0.0001$).

The comparison of ROC curves showed statistically significant differences between the areas under age curves and LARVS versus LAEF (0.198, $P < 0.0001$), as well as between the area under the ROC curve of LARVS versus that at LAEF (0.198, $P < 0.0001$).

The cut-off values identified for significant association with paroxysmal atrial fibrillation were as follows: LARVS $< 17\%$, LAEF $< 51\%$, and age > 55 years.

3.2.3. During the 3-year follow-up period, major cardiovascular events occurred in 14 (7%) of the patients with MS, namely: 8 (4%) suffered an atherothrombotic ischemic stroke, 4 (2%) an acute coronary syndrome, and 2 (1%) were hospitalized for heart failure.

Univariable regression analysis of clinical and echocardiographic parameters revealed that age, hypertension, diabetes, as well as circumferential strain and strain rate in the

common carotid arteries were significantly associated with the occurrence of major cardiovascular events.

Multivariate logistic regression analysis identified two independent predictors of major cardiovascular events, namely the circumferential strain and its velocity at the level of the common carotid arteries, $P \leq 0.01$.

Analysis of the ROC curves of these independent predictors indicated appropriate sensitivities and specificities. For the circumferential strain: AUC = 0.806, sensitivity = 82.6%, specificity = 79.2%, $P < 0.0001$), for the circumferential strain rate: AUC = 0.779, sensitivity = 82.6%, specificity = 72.4%, $P < 0.0001$). The cut-off values for predicting a major cardiovascular event were $\leq 2.9\%$ for the circumferential carotid strain and $\leq 0.35 \text{ s}^{-1}$ for its velocity.

Using these cut-off values, we obtained Kaplan-Meier survival curves, and they showed that the survival interval without major cardiovascular events, without ischemic stroke and without acute coronary syndrome, respectively, were significantly shorter in patients with low foreign values of the circumferential carotid strain and its velocity, $P < 0.0001$.

3.4. DISCUSSIONS AND CONCLUSIONS

The objectives of the study were fully met, the results obtained being positive, but especially in accordance with those in the literature.

3.4.1. The results of the first study showed that although the diameters and volumes of AS do not differ between adults with and without metabolic syndrome, AS deformity, assessed by two-dimensional speckle-tracking echocardiography, was significantly altered in the presence of metabolic syndrome ($P < 0.0001$).

Participants in this study were evaluated by hepatic elastography for the quantification of steatosis and hepatic fibrosis, as well as by conventional echocardiography and speckle-tracking for the detection of subclinical dysfunction of AS.

The originality of the study lies in highlighting a significant association between hepatic stiffness and AS stiffness in patients with MS.

Early detection of liver and heart damage in patients with metabolic syndrome is vital, as early initiation of a healthy lifestyle and appropriate treatment can prevent or delay the development of liver cirrhosis and heart failure. These measures can reduce morbidity, mortality and related costs.

3.4.2. The results of the second study demonstrate the role of echocardiography in detecting AS abnormalities in patients with TIA.

We performed a combined assessment of the size and function of AS and were able to identify the values of variables that suggest the cardioembolic etiology of TIA and indicate the need for anticoagulant therapy.

These values are similar to those published in a recent study that evaluated AS function in patients with cryptogenic ischemic stroke. The close correlation between AS and FA dysfunction may also predict AF recurrence after catheter ablation.

The study has important clinical implications because to date, the evaluation of 2D-STE has not been included in the routine examination of patients with TIA, although it would be absolutely necessary.

3.4.3. Carotid circumferential strain and its velocity have been shown to be strong and independent predictors of major cardiovascular events in adults with MS without cardiovascular disease, followed prospectively for 3 years.

Reduced deformity of the common carotid arteries detected by 2D-STE ultrasound can be used as an early indicator of cardiovascular risk in this population group.