

LUCIAN BLAGA UNIVERSITY OF SIBIU
VICTOR PAPILIAN FACULTY OF MEDICINE

ULTRASOUND B MODE EVALUATION OF COMMON
CAROTID ARTERY IN SUPRATENTORIAL STROKE

PhD THESIS ABSTRACT

Scientific guide:

Proff. Dr. MARCEL PEREANU

PhD student:

Dr. CĂTĂLIN COSMIN MUTU

2011

Contents

GENERAL PART

CHAPTER I Anatomic particularities of the cervico-cerebral circulation.....	1
CHAPTER II Physiology and pathophysiology of cerebral circulation.....	3
CHAPTER III Cerebral arteries atherosclerosis	8
3.1 Deffinitions	9
3.2 Etiologic factors of atherosclerosis.....	10
3.3 Atherosclerosis pathogenesis.....	17
3.3.1 Atherosclerosis evolution	17
3.3.2 Artery wall damage.....	18
3.3.3 Pathogenetic hypothesis.....	19
3.4 Atherosclerotic lesions staging.....	24
CHAPTER IV. Supratentorial cerebral infarction.....	30
4.1 Deffinition, epidemiology, etiology, risk factors, pathogenesis.....	30
4.2 Types of cerebral ischemia	34
4.3 Evolutive phases of cerebral ischemia.....	35
4.4 Supratentorial cerebral infarctions clinic.....	39
4.5 Supratentorial cerebral infarctions classification.....	43
CHAPTER V Cervical artery ultrasonography.....	45
5.1 General principles.....	45
5.2 Ultrasound examination.....	49
5.3 Intima-media thickness.....	51
5.4 Atherosclerotic plaques	53
5.5 Carotid artery stenosis	55

PERSONAL RESEARCH PART

CHAPTER VI Research motivation	60
6.1 Work premises	60
6.2 Work motivation	61
CHAPTER VII Research objectives.....	62
7.1 Work purpose.....	62
7.2 Research objectives	62
CHAPTER VIII Material and working methods.....	63
8.1 Patients and study design	63
8.2 Data management	64
8.3 Statistical analysis.....	66
CHAPTER IX Results	71
9.1 Synoptic presentation and homogeneity analysis of studied groups	71
9.2 Study group results and analysis.....	76
9.2.1 Demographic data.....	76
9.2.2 Risk factors results.....	81
9.2.3 Stroke subtypes.....	99

9.2.4 Intima-media thickness results	122
9.2.5 Plaque morphology results	161
9.2.6 Carotid artery stenosis results.....	173
9.3 Control group results and analysis.....	183
9.3.1 Demographic data.....	183
9.3.2 Risk factors results.....	187
9.3.3 Intima-media thickness results	195
9.3.4 Plaque morphology results	205
9.3.5 Carotid artery stenosis results.....	207
9.4 Calculation of relative risk of stroke	209
9.4.1 Risk factors analysis	209
9.4.2 Intima-media thickness analysis.....	213
CAPITOLUL X Discussion.....	217
CAPITOLUL XI Conclusion	224
CAPITOLUL XII Originality and innovative contributions of the thesis	227
CAPITOLUL XIII References.....	228
Annexes	240

Key words: stroke, atherosclerosis, stroke subtypes, carotid artery ultrasound, carotid intima-media thickness, IMT.

ABSTRACT

Stroke represents one of the leading causes of morbidity and mortality worldwide, first cause of morbidity and long-term disability in Europe, second cause of dementia and the most common cause of epilepsy in the elderly. After cardiovascular disease and cancer, stroke is the third cause of death.

This paper aims, by the information brought, to highlight the importance of ultrasound examination of the cervico-cerebral arteries both prophylactically in people presenting risk factors and in a more complete diagnostic assessment of patients with ischemic stroke.

The PhD thesis consists of two parts: a general part that contains five chapters and a personal research part, which comprises seven chapters.

Chapter I describes the anatomic particularities of the cervico-cerebral circulation, focusing on anastomotic arterial system.

Chapter II presents general dates and updated information about the physiology and pathophysiology of cerebral circulation.

In Chapter III are presented the definition, etiological factors, pathogenesis and stages of atherosclerotic lesions, focusing on cerebral artery atherosclerosis.

Chapter IV condense presents the etiopathogenesis, evolution and clinical aspects of cerebral infarctions. Here are presented the most current and widely used classifications of stroke subtypes.

In Chapter V are presented the principles of ultrasound examination of cervico–cerebral arteries and the basic indicators monitored during the examination.

In the personal research part are presented the research motivation and objectives, the aspects related to material and working methods. We reserved a large space for the chapters dedicated to the analysis results and discussion. Chapters XI and XII presents the conclusions of the research and the original and innovative contributions of these thesis, finally proposing an evaluation and prevention of stroke algorithm in patients with vascular risk factors.

International studies have shown a wide geographical variation in the incidence of stroke subtypes probably dependent on specific risk factors of the analyzed region.

More detailed study of the impact of vascular risk factors specific to our area on stroke heterogeneity can only be helpful in understanding, and thus reducing morbidity and mortality of the population of Romania.

The main goal of this paper was to establish the existence of a relationship between atherosclerotic vascular damage markers evidenced by ultrasound examination of cervical arteries and ischemic strokes pattern among the population.

Taking into consideration the aspects mentioned above, this study has the following objectives:

1. Determining the incidence of ischemic stroke subtypes according to TOAST and Bamford/Oxfordshire classifications among the patients in our geographic area.
2. Determining the risk factor profile and identifying those involved statistically significant in the appearance of each stroke subtype.
3. Comparative study of carotid intima media thickness (IMT) values in the different ischemic stroke subtypes.
4. Carotid IMT study as a vascular damage marker.
5. Establishing a correlation between carotid IMT and internal carotid artery stenosis degree in patients with stroke.
6. Analysing the predictive role of carotid IMT progression in ischemic stroke occurrence.

To achieve the goals set I performed an analytical, observational, prospective case-control type study on 607 patients (430 patients with ischemic stroke and 177 patients without stroke) admitted in the Neurology Department Sibiu between 01.01.2008 - 31.12.2009, associated with descriptive studies of the 2 groups.

In the patients studied we sought demographic issues, the presence and frequency of risk factors associated with increased relative risk of ischemic stroke, the frequency of ischemic stroke subtypes according to TOAST and Bamford/Oxfordshire classifications.

We evaluated by ultrasonography bilateral carotid IMT, the morphology and thickness of stroke ipsilateral atherosclerotic plaques, same as artery stenosis degree consecutive to their presence in the internal carotid artery, trying to emphasize the correlations between risk factors, ischemic stroke subtypes, carotid IMT, morphology of atherosclerotic plaques and carotid stenosis degree.

Likewise, I tried to identify a correlation between the progression of carotid intima-media thickness and increased relative risk of ischemic stroke.

Data were analyzed comparatively with a control group and descriptive between the groups.

The study group consisted of 430 patients with supratentorial stroke, hospitalized during the given time, to which I made the vascular risk factors inventory, the classification into stroke subtype and carotid ultrasound examination, the information obtained being recorded in a customized patient record.

The control group consisted of 177 patients without stroke, hospitalized during the given time, to which I made the vascular risk factors inventory and carotid ultrasound examination, the information obtained being recorded in a customized patient record.

The two groups were homogeneous, with no significant differences regarding: source environment, distribution by sex and age categories.

The risk factors pursued were: smoking, alcohol consumption (no / yes / occasionally), hypertension, dyslipidemia, diabetes, obesity, atrial fibrillation, and history of myocardial infarction and stroke.

Monitored laboratory findings were: systolic blood pressure, diastolic blood pressure, cholesterol, triglycerides and blood glucose on admission.

Ultrasound examination of carotid axis was performed with an ESAOTE MYLAB 50 device. Common carotid arteries, external carotid and bilateral cervical segment of internal carotid were evaluated, including the ophthalmic artery in cases where it was necessary to specify the ultrasound diagnosis.

Monitored indicators during ultrasound examination were: carotid IMT measurement, thickness and morphology of atherosclerotic plaques and assessing the arterial stenosis degree.

The classification into stroke subtypes was based on two classifications.

According to Bamford/Oxfordshire clinical-imaging classification (1991) strokes were divided in four subtypes:

- TACI = total anterior circulation stroke
- PACI = partial anterior circulation stroke
- LACI = lacunar stroke
- POCI = posterior circulation stroke.

According to TOAST etiopathogenic classification (1993), strokes were divided into five subtypes:

- LAA = large artery atherosclerosis
- SAA = small artery occlusion
- CE = Cardioembolism
- OE = stroke of other determined etiology
- UE = stroke of undetermined etiology.

Based on the informations present in the patient's research record a database that was used for statistical processing was created. Statistical processing was done with the IBM SPSS Statistics version 19.

For statistical description of the two groups we used univariate analysis and stratified data analysis, taking into account the general demographic parameters of the studied group. Differences between the two groups were analyzed by t-test function. In the correlation analysis we used the Pearson correlation coefficient. For significant risk factors we used bivariate and multivariate analysis and "odds ratio" with 95% confidence limits and p-value were calculated. The level of statistical significance for all statistical tests performed was set at a p-value = 0.05.

The study pursued three major aspects: the incidence of ischemic stroke subtypes in the studied population, the analysis of vascular risk factors and analysis of carotid intima-media thickness in terms of stroke risk.

The distribution of patients according to Bamford/Oxfordshire clinical-imaging classification of stroke is shown in the table below.

Bamford stroke subtype	Number of patients	Frequency
Total anterior circulation stroke (TACI)	25	5.81%
Partial anterior circulation stroke (PACI)	199	46.28%
Lacunar stroke (LACI)	121	28.14%
Posterior circulation stroke (POCI)	85	19.77%
TOTAL	430	100%

The distribution of patients according to TOAST etiopathogenic classification of stroke is shown in the table below.

TOAST stroke subtype	Number of patients	Frequency
Large artery atherosclerosis (LAA)	136	31.63%
Small artery occlusion (SAA)	107	24.88%
Cardioembolism (CE)	48	11.16%
Stroke of other determined etiology (OE)	6	1.4%
Stroke of undetermined etiology (UE)	133	30.93%
TOTAL	430	100%

The estimation of **relative risk of ischemic stroke in patients exposed to certain vascular risk factors** was one of the objectives of this study.

To calculate the relative risk of stroke we determined the distribution of vascular risk factors both in all patients examined and on each group, following the presence or absence of ischemic stroke.

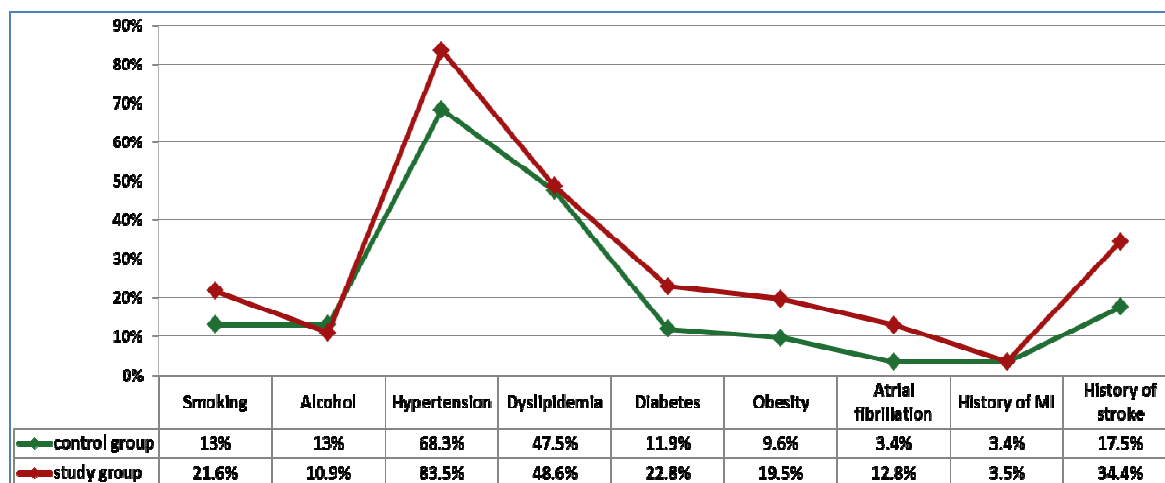


Fig. 1 The distribution of vascular risk factors between the two groups studied

To determine the association between each risk factor and the likelihood ratio of ischemic stroke we calculated odds ratio (the probability of suffering stroke related to the probability of not suffering stroke in patients exposed to risk factors).

Finally, the relative risk of stroke in patients exposed to a risk factor dependent and independent of the presence of other vascular risk factors is summarized in the following table.

Risk factor		OR (dependent)	OR (independent)
Smoking		1.85	2.27
Alcohol	occasionally	1.27	-
	high intake	0.93	-
Hypertension		2.34	1.99
Diabetes		2.19	2.01
Dyslipidemia		1.04	-
Obesity		2.28	1.99
Atrial fibrillation		4.18	4.55
History of stroke		2.47	2.43
History of myocardial infarction		1.03	-

The estimation of **relative risk of stroke in patients with increased carotid IMT** was another objective of this study.

In our study, increased carotid IMT in patients with stroke had a diagnostic sensitivity of 95.3%. The deficiency of its use as a diagnostic test for predicting the occurrence of stroke is given by its low specificity, 13%, associated with an increased rate of false positives. As a diagnostic test, carotid IMT increase over normal has a positive predictive value for subsequent occurrence of stroke of 27.8%.

Increased carotid IMT above the normal produces an increment of the risk of ischemic stroke by about 3x (OR = 3.0617, 95% CI: 1.635 to 5.733).

Thus, in our study, each 0,1 mm increase above the normal carotid IMT value produces a proportional increase of the relative risk of stroke, as seen in the table below.

Carotid IMT increment	OR	95% Confidence Interval	
		Lower limit	Upper limit
0,9-1 / <0,9 mm	1.92	0.934	3.933
1-1,1 / <0,9 mm	1.99	1.035	3.825
1,1-1,2 / <0,9 mm	2.36	1.253	4.43
1,2-1,3 / <0,9 mm	2.67	1.431	4.992
1,3-1,4 / <0,9 mm	2.79	1.496	5.216

The study's conclusions were:

1. According to TOAST etiopathogenic classification, the incidence of stroke subtypes in patients from Sibiu District was as follows: large artery atherosclerosis 31.63%, 11.16% cardioembolism, small artery atherosclerosis 24.88%, 1.4% other determined etiology, undetermined or multiple etiology 30.93%. These values overlap those in the literature, except for stroke of undetermined etiology with a higher incidence in our country probably due to low diagnostic efficiency specific to our region.
2. According to Bamford/Oxfordshire clinical-imaging classification the incidence stroke subtypes was as follows: 28.14% lacunar stroke, partial anterior circulation stroke 46.28%, 5.81% total anterior circulation stroke, posterior circulation stroke 19.77%.
3. The most frequently encountered vascular risk factor in patients was hypertension (83.5%), followed by dyslipidemia (48.6%), history of stroke (34.4%), diabetes (22.8%), smoking (21.6%), obesity (19.5%), atrial fibrillation (12.8%), increased consumption of

alcohol (10.9%) and history of myocardial infarction in 3.5% of cases. This distribution is similar to published data, except for atrial fibrillation with an almost double incidence among the patients in our study.

4. Smoking ($p = 0.038$) and atrial fibrillation ($p < 0.001$) were the risk factors that contributed statistically significant to the classification of patients into the different TOAST stroke subtypes.
5. Atrial fibrillation ($p = 0.033$) was the only risk factor with statistically significant contribution to the classification of patients into the different Bamford/Oxfordshire stroke subtypes.
6. Vascular risk factors that have increased the relative risk for stroke occurrence, in order of importance, were: atrial fibrillation (OR = 4.55), history of stroke (OR = 2.43), smoking (OR = 2.27), diabetes (OR = 2.01), hypertension (OR = 1.99) and obesity (OR = 1.99).
7. In the studied group occasionally or low alcohol consumption was associated with a slightly increased relative risk of stroke (OR = 1.27), while high alcohol intake was associated with a slight reduction of stroke risk (OR = 0.93).
8. Average carotid IMT value was higher in patients with stroke than those without stroke, in the left carotid axis compared with the right axis and in the common carotid artery on the same side with the stroke, in these cases the difference between carotid IMT values being statistically significant ($p = 0.001$).
9. Increased carotid IMT was associated statistically significant with patient age ($p < 0.0001$), patient gender ($p < 0.0001$), hypertension ($p = 0.005$) and smoking ($p = 0.02$), independent of the presence or absence of stroke, confirming carotid IMT status of independent marker of vascular damage.
10. The association between carotid IMT value and stroke subtypes had high statistically significance for both TOAST ($p < 0.00001$) and Bamford/Oxfordshire classifications ($p = 0.021$), increased carotid IMT being better correlated with stroke due to large vessel disease and lesser with lacunar infarctions.
11. The relationship between carotid IMT values and atherosclerotic plaque had high statistical significance ($p < 0.0001$), carotid IMT progression being correlated both with

atherosclerotic plaque thickness and with its inhomogeneous appearance, independent of the presence or absence of stroke.

12. The relationship between carotid IMT value and the degree of internal carotid artery stenosis is statistically significant in all patients investigated by ultrasound ($p < 0.001$), especially in patients with stroke, thus confirming that the risk of stroke in patients with asymptomatic stenosis of the ICA is augmented by the presence of an increased carotid IMT.
13. Carotid IMT increment above the normal values has positive predictive value of 27.8% for subsequent occurrence of stroke, with a sensitivity of 95.3% and only 13% specificity.
14. Carotid IMT increment above the normal value produces an increase of the risk of ischemic stroke by about 3x (OR = 3.0617, 95% CI: 1.635 to 5.733).
15. Each 0.1 mm increase above the normal carotid IMT produces a proportional increase in the relative risk of stroke between 1.9x and 2.8x (OR=1.92 for the range 0.9-1 mm, OR=1.99 for the range 1-1.1 mm, OR=2.36 for the range 1.1-1.2 mm, OR=2.67 for the range 1.2-1.3 mm, OR=2.79 for the range 1.3-1.4 mm).

The original contribution of this thesis is by representing the first scientific paper in Romania who managed to assess the incidence of ischemic stroke subtypes and vascular risk factors specific profile for this region, in the context that international studies show that there is a large geographical variability of stroke subtypes incidence, probably dependent on the risk factors specific to the analyzed region.

The calculation of the relative risk of stroke occurrence, induced by the presence of vascular risk factors specific to our geographic area and the detailed study of the impact of these factors on stroke heterogeneity can only contribute positively to the understanding and thus reducing morbidity and mortality due to vascular causes of the Romanian population.

Secondly, to obtain information that is highly predictive for the occurrence of stroke by studying markers of vascular damage (carotid IMT in this case), using ultrasound examination of the cervico-cerebral arterial system, is an important step to guide health services to prevention.

This paper is, on our knowledge, the only research in Romania and among the few international studies that have aimed to quantify the predictive aspects of carotid IMT

increment in ischemic stroke occurrence by calculating the sensitivity and specificity of this marker as a predictor of stroke.

The large number of subjects included in the study, 607 patients, and their rigorous and complex examination, detailed and accurate analysis of the information obtained allows us to state that this work meets the requirements of a representative study for the population of Romania.

Finally, the innovative and original aspect of this paper is augmented by the setting up of an evaluation algorithm for the patients with vascular risk factors and stroke prevention focused on ultrasound examination of the cervico-cerebral arteries, relatively cheap examination but effective in revealing of predictive markers for vascular morbidity.