Comparison of the magnetic resonance imaging and acoustocerebrography signals in the assessment of focal cerebral microangiopathic lesions in patients with asymptomatic atrial fibrillation. (Preliminary clinical study results)

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Acoustocerebrography (ACG) is a set of techniques designed to capture states of human brain tissue, and its changes. It is based on noninvasive measurements of various parameters obtained by analyzing an ultrasound pulse emitted through the human's skull.

ACG and Magnetic Resonance Imaging (MRI) results were compared in a clinical study assessment of focal white-matter-lesions (WML) in the brains of patients with asymptomatic atrial fibrillation (AAF). The clinical study included 55 patients (age 66.1 ± 6.7 years). According to MRI data, the patients were assigned into four groups depending on the number of lesions: L0 - 0 to 4 lesions, L5 - 5 to 9 lesions, L10 - 10 to 29 lesions, and L30 - 30 or more lesions. As a result, it has been concluded that the ACG method could clearly differentiate the groups L0 (with 0 ÷ 4 lesions) and L30 (with more than 30 lesions) of WML patients. Fisher's Exact Test shows that this correlation is highly significant ($p < 0.001$).

ACG seems to be a new, effective, method for detecting WML for patients with AAF and can become increasingly useful in both diagnosing, and in stratifying, them. This, in turn, can be helpful in individualizing their treatment, so that the risk of strokes may become essentially reduced.

Keywords: *ultrasounds, dispersion, brain, atrial fibrillation, stroke*

1. Introduction

In the last 20 years, atrial fibrillation (AF) has become one of the most important public health problems, and a significant cause of increasing health-care costs in Western countries. Atrial fibrillation is a common, and treatable, risk factor for stroke (Wolf, [WP1991]). AF is a cardiac arrhythmia that induces not only ischemic strokes, but also focal cerebral white-microangiopathic-lesions (WML) and cerebral-micro-bleeds (CMB). In the general population, around 10–20% of AF patients may have CMB, and up to 30% of AF patients with a prior stroke [7]. CMB may identify a subgroup at higher risk of intra-cerebral bleeding, but the majority of these patients with AF benefit from anticoagulation. One systematic review proved that while overall stroke risk seems doubled in patients with CMBs, the risk for intra-cerebral-hemorrhage (ICH) increased up to eight-fold [2]). Advances in the access to, and in the performance of, brain magnetic-resonance-imaging (MRI) have led to an increased detection of asymptomatic abnormalities in the brains of patients with cardiovascular diseases. White matter lesions are frequently observed on brain MRI of the elderly people, and are associated with increased risks of developing depression, stroke, and dementia [2, 4, 10]. In the general population, the prevalence of white matter hyperintensities ranges from 11-21% in adults aged around 64, to 94% at age 82 [13]. To conduct WML examination, a very expensive piece of equipment – MRI system, prices start at 2.5m€ - as well as time-consuming procedure (thin slices head MRI takes more than 45 minutes,) is necessary. The standard costs for such medical examination are in the range of 350€, up to 900€. This shows already the necessity of some alternative solution for AF patients.

Acoustocerebrography (ACG) is a set of techniques to capture the states of human brain tissue, and its changes. It is based on noninvasive measurements of various parameters obtained by analyzing an ultrasound pulse emitted across the human's skull. The main idea of this method relies in the relation between the tissue density (ρ), bulk modulus (K), and speed of propagation (c), for ultrasound waves in this medium. The values which are under concern are, amongst others: absorption coefficient, frequency dependent attenuation, speed of sound and tissue elasticity. Propagation speed or, equivalently, times of arriving (ToA) for an ultrasound pulse, can be inferred from phase relations for various frequencies. A very similar approach to this method was first described by Szustakowski and Piszczek [9, 6], where experiments involving a trans-cranial ultrasound densitometry system were presented. In 2000, the first data recorded during the clinical experiment was published by [5]. In this study, Mazur and his group, has examined the brain tissue of 62 patients, using only one frequency. The authors interpreted the recorded changes in the ultrasound signal as simple density changes of the brain tissue due to absence of blood, its hydrolyze or edema.

The measurement principle is simple (Fig.1). The time of arriving for the transmitted pulse through a skull, is calculated from transmission/reception phases for two sine waves with base frequencies f_1 and f_2, respectively, where T_x is the time duration of the measurement.

This rather elementary idea was modified by introducing a new multifrequency transmitting/receiving system (see Fig.3), that considerably improved the precision of the estimations of velocities and attenuations in intra-cranial tissue. Several international patents cover this new approach. We show that, using multiple frequencies, the dispersive character of the brain tissue gives brighter interpretation to the ultrasound signal alteration. For complex biological tissue, the effect of longitudinal wave dispersion - it is such an effect - in which non-linear frequency-dependent mediums bulk modulus results in different propagation speeds, for different ultrasound frequencies, is clearly observed and measured. In this

development, the major goal was not to create some more sensitive medical equipment, like MRI; but to make a semi-automatic non-invasive screening system which can save costs, time, and does not use a special skilled operator, such as a high-level radiologist, or neurologist.

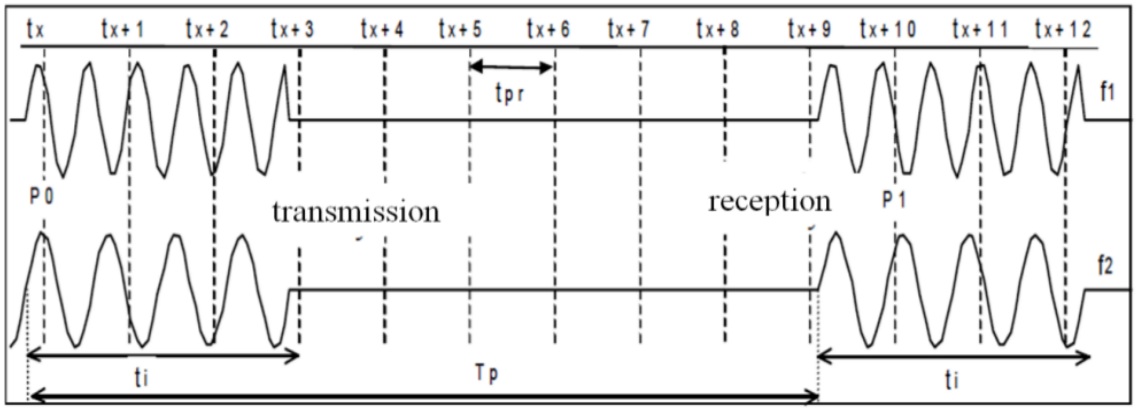

Fig. 1. The basic idea of Piszczek & Szostakowski [6, 9]: two ultrasound pulses with slightly different frequencies, f_1 and f_2, are being emitted on one side (see 1.2), and received at the other side. Then, at a definite time point T_x, the phases, φ_1 and φ_2, of both pulses are determined. Assuming lack of dispersion (the velocity of a single sinus-shaped pulse does not depend on its base frequency) and given that $0 < f_2 - f_1 < 1/T_x$,
the time of arriving (ToA) equals $T^{(A)} = T_x - \mathrm{mod}\,(\varphi_2 - \varphi_1, 2\pi) / (2\pi \cdot \Delta f)$.

This device will allow monitoring of the brain's health by the general practitioner or cardiologist, avoiding time-consuming, and expensive, MRI or CT examinations in hospitals, to check the brain's health state on a regular basis. Acoustocerebrography (ACG) is able to track the development of the brain state, almost on a daily basis.

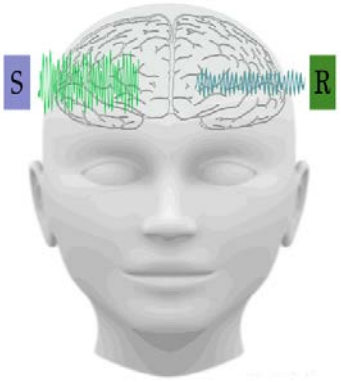

Fig. 2. Location of ultrasound transducers.

2. The assessment of cerebral lesions on MRI

In magnetic resonance imaging, WML demonstrates hypo-intense signal in T1 weighted images and hyper-intense in T2 weighted images and Fluid Attenuated Inversion Recovery (FLAIR) images (see Fig.3.). FLAIR is considered to be the most appropriate sequence to assess WML. Free fluid signal suppression provides better WML visibility and demarcation. Fluid containing lesions, such as lacunae or perivascular spaces, can be identified and differentiated from WML. Imaging was performed on a Siemens 1,5T scanner. Sagittal 3D FLAIR images (1 mm slice thickness) were used to assess the number of WML. We used semiautomatic software available on the GE Health-care Advantage Workstation 4.6 (Volume Share 5). We counted every lesion measuring at least 2 mm on each sagittal 3D FLAIR scan. Lesions that were visible on two or more scans were counted several times accordingly. Patients were classified into diagnostic groups based on the total number of lesions.

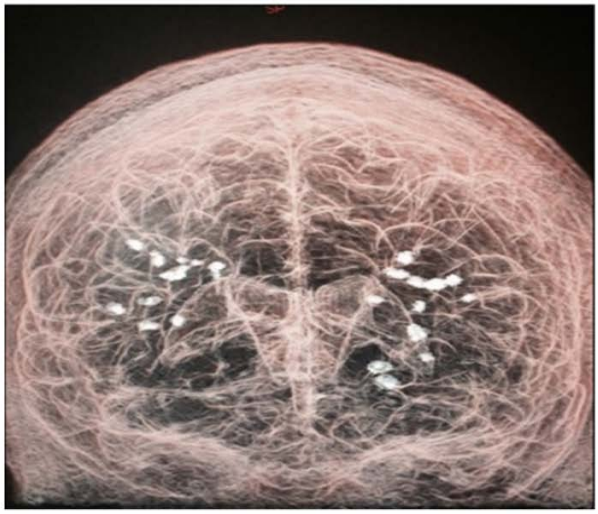

Fig. 3. Example of brain Focal Cerebral Microangiopathic Lesions (white spots) in 3D MRI reconstruction.

3. The assessment of cerebral lesions on acoustocerebrography (ACG)

All patients were examined by a doctor, then the ultrasound measurement was performed, using the multi-spectral ultrasound brain scanner Sonovum UltraEASY™. The measurement procedure was the same as described in [12]. The measurement alone took about 5 minutes, and the entire procedure for acquiring data consisted of two stages:

- A coarse approximation of frequency attenuation distribution (FAD), which consists of emitting a sequence of ultrasonic mono-spectral signals with (in advance) fixed frequencies, and receiving their echoes. This is the basis for estimating the distribution of the attenuation of ultrasonic waves, in the frequency range under consideration. As a result of that, for each of the respondents, a row of attenuation coefficients (ATN)

was obtained. In estimating the attenuation coefficients, the characteristics of the measuring device were taken under consideration.

- Thus emitting a profiled ultrasonic multi-spectral signal whose parameters (number of frequencies and their values and amplitudes) were established on the base of earlier performed experiments. The phase shifts of individual frequency components have been chosen according to specific optimization criteria; on the absolute values of peaks, their spread, and the average value of the signal. The received echo is further decomposed into single frequency components (see Fig.4), acquiring a bunch of amplitude and phase value pairs (phase vectors), each for every frequency with the use of the well-known least square method (see, for instance [8]). Afterwards, a sequence of derived parameters is determined (see [1]).

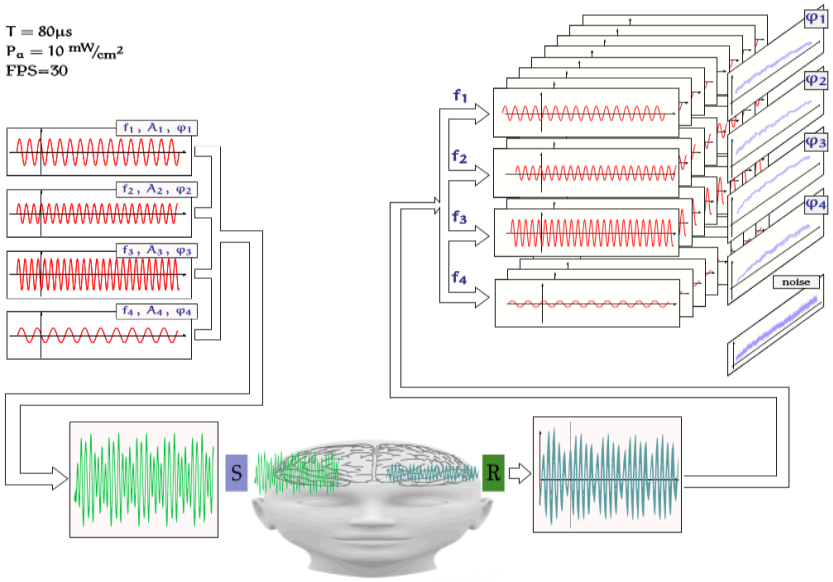

Fig. 4. An outline of the process of forming a multidimensional phase bundle: The compound multi-spectral signal is being emitted at one side of a patient's head, and after transversing skull bones and the brain tissue, it is being received on the other side. Then, the received signal is being decomposed into sine waves with base frequencies equal to the ones included in the original signal, and their phases φ_1 , ... , φ_H (here H=4) are reconstructed. Repeating this process many times, one obtains the phase bundle depicted to the right of the picture. Composing the multi-spectral input signal consists of choosing base frequencies f_1, ..., f_H (appropriately to the sampling frequency F = 96 MHz here), their amplifications $A_1^{(ini)}$, ... , $A_H^{(ini)}$ and their relative phase shifts φ_1 , . . . , φ_H . Then, the sine waves with these parameters are being summed up into the proper input signal.

4. Statistical analysis of accoustocerebrographic (ACG) data

Data for analysis is described by 266 variables, which consist of basic types of physical signal description: absorption, attenuation, amplitude, velocity, transition time through the head, elasticity of the head, measured for 10 frequencies.

The aim of the statistical analysis is classification of ACG measurements, using some diagnostically motivated groups.

In our work we used classification into ***CHA_2DS_2-VASc*** groups, as well as classification on group of lesions. ***CHA_2DS_2-VASc*** score, is a clinical prediction rule for estimating the risk of

stroke in patients with non-rheumatic atrial fibrillation (AF), a heart arrhythmia associated with thromboembolic stroke (see: http://www.mdcalc.com/cha2ds2-vasc-score-for-atrial-fibrillation-stroke-risk/ and https://en.wikipedia.org/wiki/CHA2DS2%E2%80%93VASc_score).

4.1. Selecting of predictor variables

The accoustocerebrographic data consists of 8787 variables, measured in patients. The preprocesing was provided in 3 steps:

- eliminating highly correlated variables (with correlation greater than 0.90),
- eliminating variables with high variance inflation factor
- choosing highest informative variables, using Boruta procedure
- (see: https://www.jstatsoft.org/article/view/v036i11/v36i11.pdf)

The statistically significant predictors are two variables: *stabilPhsHatspWeitefreq1*8 (variable *xx*) and $kenn_h$atfftmeanf7p1of4 (variable *yy*). Both variables were 0-1 normalized (0 is minimum and 1 is maximum value of the variables)

4.2. Classification of CHA_2DS_2-VASc score.

The ACG measurements were classified in three groups of CHA_2DS_2-VASc score: 0,1,2 (group 0-2), 3 (group 3), and 4,5,6 (group 4-6).

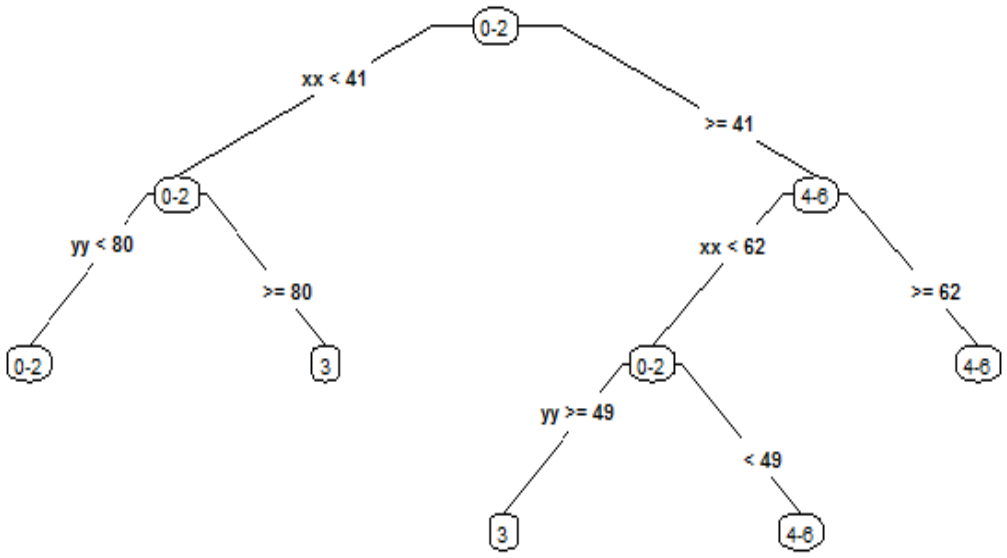

Fig. 5. Classification tree CHA_2DS_2-VASc.

4.3. Logistic classification in two groups of lesions.

To show the capabilities of ACG measurements, the logistic classificator for two groups of lesions was constructed.

Group L0 is the group of patients with less than 10 lesions, while the group L30 is the group of patients with more than 30 lesions.

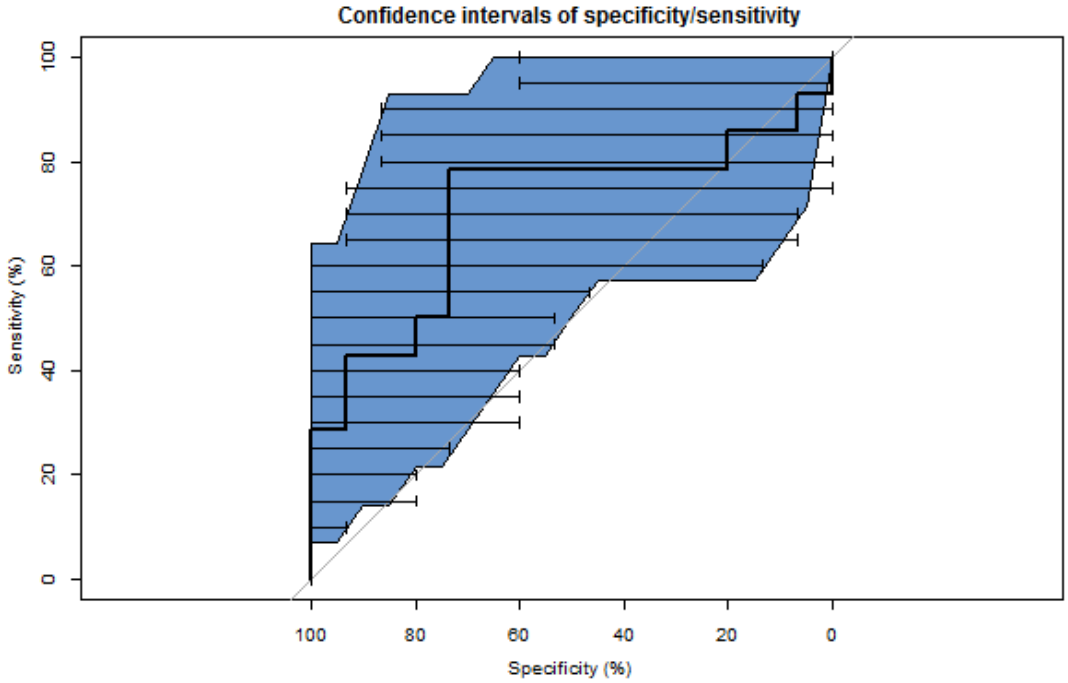

Fig. 6. ROC curve for L0 - L30 classification. The AUC under the ROC curve is 0.86.

According to MRI data, the patients were assigned into four groups based on the number of lesions: L0 – 0 to 4 lesions, L5 – 5 to 9 lesions, L10 – 10 to 29 lesions, and L30 – 30 or more lesions. As a result, it has been concluded that the ACG method could clearly differentiate the groups L0 (with 0 ÷ 4 lesions), and L30 (with more than 30 lesions), of WML patients (see Fig.2.2). Fisher's Exact Test shows (All calculations were performed using R free Open Source software environment for statistical computing and graphics: https://www.r-project.org/) that the correlation here is highly significant ($p < 0.001$).

The verification of the variables, connected with classification into the groups L0 and L30 was provided by the Boruta procedure [15]. Two attributes ToAFreq6Q2, and ToAFreq9Q2, were confirmed to be the most important within the 266 analyzed.

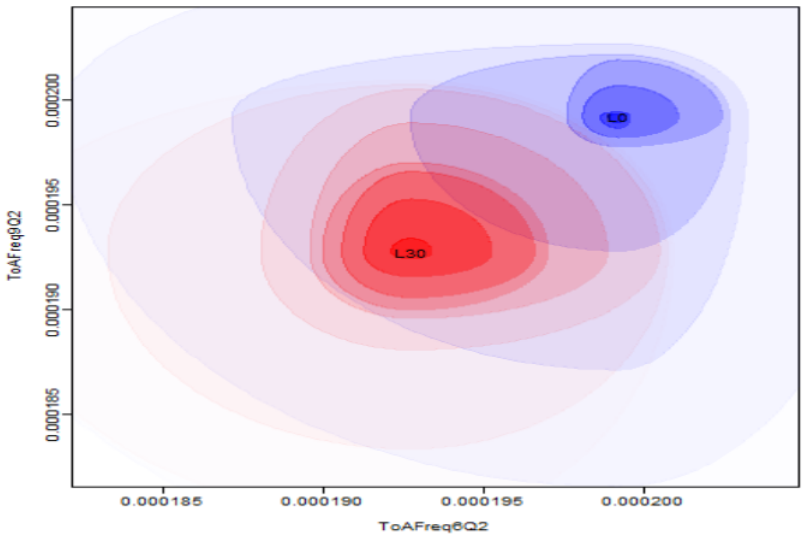

Fig. 7. Two-dimensional distribution of vector (ToAFreq9Q2, ToAFreq6Q2) in L0 (blue) and L30 (red) classes. Each ellipsoidal contour represents a pair of hexadeciles: from 7th hexadecile to 11th hexadecile, from 6th hexadecile to 12th hexadecile, from 5th hexadecile to 13th hexadecile, from 4th hexadecile to 14th hexadecile, from 3rd hexadecile to 15th hexadecile, from 2nd hexadecile to 16th hexadecile, from 1st hexadecile to 17th hexadecile. The position of class label (L0, L30) on the graph is defined by the median coordinates of vector (ToAFreq9Q2, ToAFreq6Q2). The intensity of contour color represents the level of hexadecile: the highest level corresponds to a more intensive color. The graph is the realization of Shinichiro Tomizono ellipse plot construction (https://tomizonor.wordpress.com/2013/04/29/ellipse-plot/)

5. Discussion

The present study establishes, for the first time, that the ACG signal can differentiate numbers of WML in patients with atrial fibrillation.

The aim of this study was to show that cerebrovascular changes caused by atrial fibrillation could be detected using acoustocerebrography. At the same time, no single value can be clearly associated with WML numbers. The focus of this work is not to suggest a new way for diagnostics of AF, since there are many easy and reliable procedures already known, but to show that acoustocerebrography can be a useful medical tool for detecting changes in the human brain. With new technologies and further research, acoustocerebrography might be able to perform monitoring tasks, such as early stroke detection. Even though the current system is not able to produce an image, it can detect pathologic changes of the brain, so that other steps can be immediately performed [14]. Based on the recorded and processed ultrasonic signals, the following hypothesis can be set: we have detected significant changes in the sound velocity in the brain tissue with increasing amounts of WML. We have also seen, some changes in signal attenuation (this will be the topic of the next publication). Such parameter alteration could result in the following physical interpretation: WML is more homogeneous than the surrounding tissue, which causes the increasing sound velocity of chosen frequencies. Such ultrasound velocity behavior is very well known from (e.g.) cancer research field, where even bigger sound velocity alterations are recorded during the examination of mammalian material.

6. Conclusions

ACG is a new, effective, method for detecting WML in patients with AAF, and can become increasingly useful in diagnosing, and in stratifying, patients with AAF. This, in turn, can be helpful in individualizing their treatment; so that the risk of stroke may become essentially reduced.

Limitation of the study:

- WMH can have other causes, independent of AF related changes,
- Number of WMH volume doesn't represent the volume of lesions.

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