

## Transcranial Doppler and vasodilators therapy as predictors of early outcome in acute ischemic stroke

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### Abstract

The clinical impact of risk factors and vasodilator therapy in prevention of acute ischemic stroke remains uncertain. Ischemic stroke was considered severe in the Romanian Stroke Prevention Society. Poor outcome are at 10 days after onset of a minor ischaemic stroke or a transient ischaemic attack. The association between predictors and outcome was assessed using unconditional multivariable logistic regression. Covariates used included age, stroke severity, diabetes mellitus, coronary artery disease, atrial fibrillation, premorbid hypertension and hyper-lipidemia and the results pursued by Transcranial Doppler, analyzing the Pendefunda's Index. Three hundred and twenty-eight patients were included. Compared to patients predicted as normal who were found to have an increased stroke risk, our patients decreased the clinical aspects after the vasodilators administration, while the reactivity in the first week after stroke onset was found to result in a decreased risk. However, neither of these findings remained significant after adjustment for the described covariates if we haven't test the best reactivity to the drugs.

**Keywords:** acute ischemic stroke, brain infarction, clinical management of stroke, prediction of outcome, stroke prognosis, transient ischaemic attack, minor ischaemic stroke

### Introduction

Transcranial Doppler sonography (TCD) is used to assess cerebral blood flow velocity in basal cerebral arteries and is a common tool for the diagnosis and follow-up of cerebrovascular disease. With more than hundred clinical studies using TCD published annually, indications for its use are expanding. The clinical applications for TCD including delayed vasospasm after subarachnoid hemorrhage, sickle cell disease, atherosclerosis of cranial vessels, ischemic stroke, brain trauma, brain death, carotid artery disease, cerebral venous thrombosis, intraoperative TCD monitoring, arteriovenous malformations, cardiac shunts and preeclampsia, the reactivity after vasodilators of the cerebral arteries. The relevance of acute changes in blood pressure and the impact of vasodilator therapy administered in the acute period are also uncertain. There is currently little data from randomized controlled trials to inform physicians about the management of blood pressure and its relation to patient outcome in acute ischemic stroke. Most studies assessing the impact of the risk factors in the acute period have focused on functional outcomes after a minor ischaemic stroke or a Transient ischaemic attack. Recent clinical studies have suggested that more than 75% of acute ischemic stroke patients present have

hypertension. However, despite this high prevalence, our understanding of the potential impact of the level of blood pressure in acute stroke remains incomplete. Several authors argue that elevated post-stroke blood pressure leads to poor outcome, related to increased cerebral edema and risk of hemorrhagic transformation. Alternatively, other reports emphasize a relationship between low blood pressure and poor outcome, citing threats to the ischemic penumbra. Prevention of a severe ischaemic stroke is our goal of this present study.

### Methods

We reviewed the records of all patients presenting with transient ischemic attack or a minor ischaemic stroke more than two days after symptom onset and in-hospital stroke secondary to a surgical or major medical event(s).

TCD was first used in 1981 when Aaslid and coworkers assessed middle cerebral artery cerebral blood flow velocity in patients with aneurysmal subarachnoid hemorrhage indicating vasospasm. The main difference between Aaslid's "Ur-Doppler" and other, conventional Doppler ultrasound devices at the time was that the bidirectional probe was pulsed with a lower frequency of 2 MHz in order to sufficiently penetrate the temporal bone window. Its main advantages compared to most other neuroimaging methods are convenience, mobility, low cost, non-invasiveness, and lack of side-effects. The TCD technique is noninvasive and can easily be repeated bedside without any risk for the patient. The agility of the TCD equipment has also raised hopes for ultra early assessment of intracranial dynamics following head injury. However, the results of a TCD

examination depend on the experience and diligence of the examiner. Clinicians need to follow these developments but should also beware of their often somewhat limited practical value. To assess the usefulness of TCD, it is impracticable or simply not applicable to perform blinded, randomized or placebo-controlled studies. Yet, guidance for using TCD should be obtained from prospective studies with sufficiently large patient samples and with a reasonably simple and reproducible technique. Our studies fulfilling the criteria of broad study population, validation of TCD by comparison to the other researches, blinded evaluation of the data and statistically dependable diagnostic or prognostic value.

The value of TCD recordings in patients with head injury is, however, controversial even though changes in flow velocities may enable early detection of potentially treatable cerebral blood flow disturbances. We introduced new methods in our clinic in 1987 and then developed them in Freiburg between the years 1988-89, introducing new indices for the evaluation of the cerebral blood flow. One investigator conducted all TCD examinations.

The daily TCD measurements were conducted transtemporally using a traditional 2-MHz transducer (EME TC-64 Eden medical records, Uberlingen, Germany). The TCD measurements were routinely performed bilaterally on the middle cerebral artery and vertebral basilar arteries. Recordings were pursued analyzing the Gosling's Pulsatility Index (PI) calculated according to the method of Gosling derived from the difference in the systolic and diastolic flow velocity. Then the PI data were correlated to the results after vasodilators administration related to the Pendefunda's Reactivity Index (RI)

described in 1988. There are more than twenty years that this index, which I described, was used, because I considered necessary an easy evaluation of the vascular replay to a drug administration.

### Technique

In addition to the medical indication to perform TCD, subjects need a sufficiently thin temporal bone window to enable penetration of the 2 MHz waves. The temporal window is suitable for insonation in more than 90% of patients, but may become more difficult to penetrate in older patients, which prompted the development of a 1 MHz probe. TCD permits evaluation of the MCA, anterior cerebral artery (ACA), posterior cerebral artery (PCA) and terminal internal carotid artery (ICA). The suboccipital (transforaminal) insonation can be performed on a supine or sitting patient and yields good accessibility of the basilar artery (BA) and possibly the vertebral arteries (VA). A transorbital approach can be used to insonate the ICA in the carotid siphon and the ophthalmic artery. Unless stated otherwise, cerebral blood flow indicates mean flow velocity. Ample reference values for it, proper angle and depth of insonation are provided for healthy subjects, including stratifications for age and sex. Cerebral blood flow obtained by TCD devices is a result of a spectrum of waves reflected by erythrocytes, and thus depends particularly on hemorheological conditions. In patients with very low hematocrit (under 30%), the velocity is increased due to a decrease in viscosity. Thus, TCD interpretation in patients with abnormal blood viscosity requires caution. An insonation of all accessible arteries can help distinguish between a systemic cause of increased velocity (fever,

hematocrit) or a focal increase suggesting a local abnormality. Moreover, sufficient time to perform a thorough examination and experience are key factors contributing to its accuracy.

Patients were categorized into those who continued to receive antihypertensives for more than five days out after the transient ischaemic attack or minor ischaemic stroke onset versus those who did not. Patients received AHT as per the clinical judgment of the treating neurology team. Antihypertensive medications included:  $\alpha$ -adrenergic receptor blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers,  $\beta$ -adrenergic receptor blockers, calcium antagonists, diuretics, centrally acting agents (including *amethyldopa* and *clonidine*), nitric oxide donors, *Cerebrolysin* or *Actovegin*.

Comorbidities, including history of coronary artery disease, atrial fibrillation, substantial carotid stenosis, chronic hypertension, diabetes mellitus, and hyperlipidemia were recorded using patient histories as documented by the neurology team. In the case of hypertension, diabetes mellitus and hyperlipidemia, premorbid and hospital discharge use of disease-modifying therapy was also used in defining these conditions. Atrial fibrillation was defined as any evidence of atrial fibrillation on history or by electrocardiography. Substantial carotid stenosis was defined as more than 50% narrowing of one or more extracranial vessels as documented by carotid Doppler.

### Results

With repeated carotid Doppler sonograms, Steiger investigated PI in patients with severe head injury as compared to healthy volunteers. This

extracranial utilization of PI revealed values between 1.5 to 2.0 in control subjects with a gradual increase in cases with posttraumatic brain edema. PI values were associated with severe intracranial hypertension, and in cases of angiographically demonstrated cerebral circulatory arrest, PI values in the range of 6 to 8 were found. RI was present in a significant correlation between PI and the risk factors we found.

The correlation are stronger as compared to previous studies. Homburg investigated 10 head injured patients and demonstrated a positive exponential correlation between PI and the blood pressure. McQuire and colleagues performed TCD measurements within 3 hours after injury on 22 head injured patients. Moreno correlated TCD measurements and found that an elevated PI predicts poor outcome, and furthermore, we saw a good reactivity in the larger arteries but different between the same in right or left side, different for the same drug to each patient, more after a minor stroke or a transient ischaemic attack. These findings strongly suggest the presence of high distal vascular resistance in the early phase after head injury. The authors also showed that one-third of patients with severe head injuries have vasospasm, and that vasospasm will significantly change both PI and RI. In our study we found that RI reflects the best drug we may administer to a patient, different from one to another and the poor reactivity in the case of a reduced volume flow in the insonated artery, and can hence be helpful to indicate compromised cerebral perfusion. This aspect should guide the choice of a medication able to prevent a new attack. The differences between the drugs we presented in a lot studies in these

twenty four years.

Our results demonstrate that RI may be influenced by different factors, like hemodynamic, respiratory, and hematologic parameters, and, in the case of brain vessels, tissue compliance. For this reason, the absolute value of this index is, in general, not considered sufficient to characterize overall intracranial hemodynamic conditions if no other information is simultaneously provided. The main advantage of RI is that, being a ratio, it is not affected by the pressure created by the heart, but in the arterioles the normal mean pressure drops. During elevated intracranial pressure, the arterioles are easily compressed creating a high peripheral vascular resistance reducing the flow, and thereby, the denominator of the PI after and before the administration of the drug. The numerator of the PI derives from the difference between systolic and diastolic flow velocities. The elasticity of the normal vascular system dampens the flow and flow velocity fluctuations because of blood pressure changes, which is in contrast to a rigid tube where the pressure is directly proportional to the flow velocity. A clinical setting where this is apparent is the elevation of PI in diabetic patients with cerebral microangiopathy and hence depressed vessel compliance. An increased intracranial pressure always results in reduced compliance of the entire brain tissue including increased rigidity of the brain arteries augmenting the velocity variations, which in turn increases the PI. Consequently, the great difference between two TCD measurements (a major RI) reflects the changes in the peripheral resistance and the benefits of the vasodilator used. The flow velocity pattern in cerebral arteries is affected both by

cerebrospinal fluid pulsatility and the reactivity of cerebrovascular control mechanisms. The different risk factors pursued by us showed that atherosclerosis was the worst for the prognostic because the reactivity of a such an artery is practically zero.

### Discussion

In the present study, we observed a relationship between initial PI and early functional outcome and survival as determined at two weeks after ischemic stroke onset. Poorest outcome was among those with a low RI. This finding remained valid when analyzed in a continuous quadratic model. In addition, these results remained significant after adjustment for multiple covariates including age, initial stroke severity, premorbid history of hypertension, hyperlipidemia, diabetes mellitus, coronary artery disease, atrial fibrillation and substantial carotid stenosis.

Other previous studies have demonstrated similar relationships. Some authors have suggested that levels of blood pressure in the acute post-stroke period increase with initial stroke severity in a compensatory fashion to ensure perfusion of the ischemic territory and that Pendefunda's Index suggest a better medication. These authors conclude that the relationship between elevated blood pressure and poor outcome is not a causal one. This would suggest that the initial level does have an effect on short-term outcome that appears to be independent of the initial stroke severity.

The our study the elevations of RI more than 15% in the first 24 h may assure good results. On the other hand, some authors have reported that substantial decreases in early blood pressure levels can also be

strong predictors of poor outcome. These findings, at first contradictory, would be consistent with the rationale that, while moderate decreases in levels of blood pressure are protective against hemorrhagic transformation and cerebral edema, excessive acute decreases may threaten the ischemic penumbra. This interpretation is consistent and we emphasize a limited and gradual increase in the RI in the acute period. However, our findings may suggest that equally important recommendations should be made to search the best vasodilator after the attack in order to have good results in caring and preventing a major stroke.

### Conclusion

Our datas show a highly significant correlation between the increased rate of risk factors for the early outcome of an ischaemic head injury and the pursuit of the RI to prevent a major stroke. Compared to patients predicted as normal who were found to have an increased stroke risk, our patients decreased the clinical aspects after the vasodilators administration, while the reactivity in the first week after stroke onset was found to result in a decreased risk. However, neither of these findings remained significant after adjustment for the described covariates if we haven't test the best reactivity to the drugs.

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