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Regular Article

Association of elevated plasma viscosity with small vessel occlusion in ischemic cerebral disease

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ABSTRACT

Introduction: Elevated plasma viscosity (PV) is observed in patients with vascular risk factors, such as diabetes mellitus or arterial hypertension. In this study we investigated the association of plasma viscosity and the different clinical and radiological entities of cerebral ischemia.
Methods: PV of 465 consecutively admitted patients with clinical symptoms of acute cerebral ischemia without radiological signs of bleeding was measured. Data is expressed as median [range] unless stated otherwise. $p < 0.05$ was considered statistically significant.
Results: Patients with acute cerebral ischemia (TIA or Stroke) showed increased PV (TIA 1.27mPas [1.07-1.53], stroke 1.27mPas [1.07-1.56]) compared to patients without cerebral ischemia (Mimics) (1.23mPas [1.06-1.42]). The group with radiologically proven small vessel disease (SVD) had a significantly higher mean values of PV (1.29mPas [1.06-1.54]) compared to those with signs of large vessel disease or cardioembolic events (1.22mPas [1.07-1.56], $p < 0.001$).
Patients with chronic heart failure ($p = 0.007$), arterial hypertension ($p < 0.001$) and diabetes mellitus ($p = 0.002$) had higher PV compared to patients without these cardiovascular risk factors. Hyperlipidemia or nicotine abuse showed no relation to PV.
Conclusion: Elevated PV is not only associated TIA and Stroke but is also found in patients with radiological signs of cerebral SVD. High levels of PV could be an underestimated risk for TIA and Stroke and participate in the complex pathophysiology of SVD. Prospective observational and interventional studies are warranted for further evaluation of PV in neurological ischemic diseases.

Introduction

Plasma viscosity (PV) is a mechanical property of plasma and describes inner attrition. It is a proportionate physical constant, dependent on the mixture and modification of plasma proteins including lipoproteins as well as on an individual's level of hydration [1,2]. Proteins with significant impact on PV are characterized by their high molecular weight and include IgM, α_2-macroglobulin and fibrinogen. Smaller proteins, like albumin, have minor relevance for changes in PV. For physical measurement and calculations, plasma is assumed to be a nearly newton's fluid due to the absence of particles [3,4]. The most common unit is milli-Pascal-second (mPas).

Normal PV values range between 1,10-1,35mPas [3] or 1,14-1,34mPas [5]. With regard to fluid dynamics of the terminal vascular bed, the relevance of PV becomes apparent. In capillary blood vessels, overall blood fluidity is highly dependent on PV due to the increased interaction of cells with plasma (Fåhræus-Lindqvist-Effect) [6]. In vessels smaller than 300 μm, erythrocytes are deformed and pass singularly through the capillary bed. By this, effective hematocrit is lowered and plasma viscosity becomes the major determinant of fluidity [7].

Elevated PV was recognized as a risk factor for vascular events [8]. An increase of PV by one standard deviation (PV > 1,29mPas) leads to a two-fold risk of vascular obliteration [9]. Schneider et al. showed increased values of PV in eight patients with M. Binswanger (SAE) [10].

Furthermore elevated PV was associated with various diseases including chronic heart failure, hypertension, diabetes mellitus and obesity [4,8,9]. The influence of smoking on PV is still debated, as studies are inconclusive [8,11].

In this study PV was measured in patients with clinical signs of acute cerebral ischemia. The aim of the study was to identify the frequency of altered PV in relation to different cerebral ischemic lesions and mimics.

Abbreviations: CCT, cranial computer tomography; ECG, electro cardiogram; LVD, large vessel disease; mPas, milli-Pascal-second; MRI, magnet resonance imaging; PV, plasma viscosity; SAE, M. Binswanger/subcortical arterial encephalopathy; SVD, small vessel disease; TIA, transitory ischemic attack.

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Methods and design

Patients

We enrolled 465 consecutive patients from the neurological emergency department of Klinikum Saarbruecken (Germany) suffering from clinical signs of acute cerebral ischemia according to the established Manchester Triage System. Diagnoses were based on clinical findings of an experienced neurologist and radiological signs in CT or MRI. Cardiovascular risk factors (chronic heart failure, arterial hypertension, diabetes mellitus, hyperlipidemia, smoking) were documented. Patients with onset of symptoms prior to 24 hours were excluded from the study.

Study design

All patients received immediate cerebral imaging with CCT and/or MRI, standard blood sampling, ECG and chest x-ray.

Diagnosis was based on clinical examination, radiological signs of acute cerebral lesions and additional diagnostic tests like echocardiography and duplex sonography of the carotid and vertebral arteries. The patients were classified clinically in groups of TIA or Stroke. Patients with other cause of acute neurological disease (i.e. epilepsy, Todd`s paresis, migraine) were classified as Mimics. This resulted in three mutually exclusive clinical groups.

According to the results of CT/MRI, patients were furthermore classified based on the presence of radiological-pathological entities 1) small vessel disease (SVD), 2) cardioembolic lesion, 3) large vessel disease (LVD) and 4) no lesion. Co-classification into several groups was allowed if there were signs supporting different pathological entities.

The radiologist was briefed to describe every sign of cerebral ischemia independent of the clinical signs of acute neurological deficit and age of imaged lesions. Both occurrence and absence of pathological findings had to be described.

The study complies with the declaration of Helsinki and was approved by the local ethics committee.

Measurements of PV

Measurement of PV was integrated into clinical routine. EDTA plasma was collected separately by peripheral venous puncture within four hours of admission. Samples were processed by centrifugation at 3000 ×*g* for 20 minutes at 20 °C. PV was determined in all patients within 24 hours of onset of symptoms.

PV was measured with a capillary tube viscosimeter (KSV6, Rheomed GmbH, Heppenheim, Germany) according to instructions of the company [12]. Reference values were defined between 1.14-1.34mPas [5,13].

Statistics

Data was processed using Microsoft Excel® for storage and basic calculations. Statistical calculations were performed by Gigawiz Aabel version 3.0.3. Continuous variables were tested for normality and groupwise for variance homogeneity by Shapiro-Wilk test and Hartley´s F_{max} test respectively. The majority of the data was non-normally distributed and is thus expressed as median and range unless stated otherwise. Differences between groups were tested by Mann-Whitney U test for non-normally distributed variables. For boolean variables contingency tables were created and evaluated by the Chi-square-test. All tests were two-sided and a p-value of less than 0.05 was considered statistically significant.

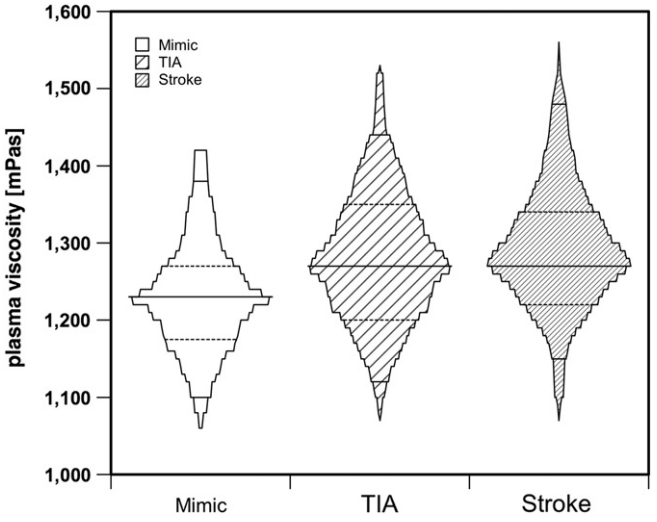

Fig. 1. PV in patients suffering from Mimic, TIA or stroke (infarction) (see Table 2).

Results

The demographic data of the patients, neuroradiological investigations and diagnosis are outlined in Supplemental Table 1. PV in patients with stroke (1.27 [1.07-1.56], n = 259) or TIA (1.27 [1.07-1.53], n = 138) was significantly higher compared to patients presenting with mimic (1.23 [1.06-1.42], n = 68, Fig. 1).

Cerebral ischemia and PV

Patients were classified into groups of high (≥1.26mPas) or low (<1.26mPas) PV. The median of PV of the whole study cohort at 1.26mPas served as cut-off. Stroke was associated ($p = 0.02$) with high PV, however this could not be demonstrated for patients suffering from TIAs. The group of patients classified as Mimics showed significant more often PV below 1.26mPas ($p < 0.001$, Table 1).

Patients with SVD were significantly ($p < 0.001$) more frequently found in the group of patients with PV above 1.26mPas rather than in the group with low PV. No difference of PV was found in patients diagnosed suffering from cardioembolic lesions or large vessel disease (Table 1).

Vascular risk factors and PV

Patients suffering from chronic heart failure ($p = 0.007$), hypertension ($p < 0.001$) or diabetes mellitus ($p = 0.002$) had significantly higher PV compared to patients without these risk factors. No differences of PV were found in patients with hyperlipidemia or nicotine abuse (Table 2).

Table 1
Comparison of PV between clinical and radiological subgroups of the patient cohort.

	PV < 1.26mPas	PV ≥ 1.26mPas	
n	209	256	
Mimic	47 (22.5%)	21 (8.2%)	p < 0.001
TIA	58 (27.8%)	80 (31.3%)	n.s. (p = 0.411)
Stroke	104 (49.8%)	155 (60.5%)	p = 0.020
TIA and Stroke	162 (77.5%)	235 (91.8%)	p < 0.001
SVD	118 (56.5%)	211 (82.4%)	p < 0.001
LVD	65 (31.1%)	95 (37.1%)	n.s.
Cardioembolic lesion	71 (34.0%)	86 (33.6%)	n.s.