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Influence of blood viscosity to cerebral blood flow in older humans compared to young subjects

Ruth F. Santos-Galduróz [a,b], Orlando F.A. Bueno [c], Lilian I. Yamaga [d], Fernanda Armani [c], José Carlos F. Galduróz [c,*]

[a] Department of Biosciences, Universidade Estadual Paulista, Rio Claro, SP, Brazil
[b] Center for Mathematics, Computing and Cognition, Universidade Federal do ABC, Santo André, SP, Brazil
[c] Department of Psychobiology, Universidade Federal de São Paulo, UNIFESP, SP, Brazil
[d] Hospital Israelita and Research Institute Albert Einstein, SP, Brazil

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HIGHLIGHTS

- Blood viscosity (BV) is one of the most important factors determining blood flow.
- The elderly have a lower blood flow than the young.
- The impairment in cerebral blood flow observed in the elderly volunteers might be due to an increase in BV.

ABSTRACT

Objective: Since blood viscosity (BV) is one of the most important factors determining blood flow, this study aimed to investigate the possible correlation between increased blood viscosity and reduction of regional cerebral blood flow (rCBF) in healthy ageing.
Methods: Male subjects were distributed in two groups: "young", aged 20–30 (27 volunteers), or "elderly", aged 60–70 (50 volunteers). Whole blood viscosity was obtained with a Wells-Brookfield Cone/Plate Viscometer. Cerebral blood flow was analysed by means of single photon emission computed tomography (SPECT).
Results: The mean BV values were 3.28 ± 0.43 mPa in the group of young volunteers and 4.33 ± 0.73 mPa in the group of elderly volunteers ($t = -6.9$, $p < 0.0001$). The elderly had a lower blood flow than the young in the following regions: bilateral parietal; temporal–parietal and temporal of the left hemisphere. Pearson's correlation between BV and rCBF showed a good inverse correlation when the BV was above 3.95 ± 0.83 mPa.
Conclusions: Our results point to a close relationship between the two parameters analysed, BV and rCBF. The impairment in rCBF observed in the elderly volunteers might be due to an increase in BV, among other factors.
Significance: These findings suggest interesting possibilities for the treatment/prevention of brain ageing.

1. Introduction

Blood viscosity (BV) is one of the most important factors determining blood flow, since increased viscosity tends to reduce blood flow in accordance with Poiseuille's law (Lowe et al., 1980; Marcinkowska-Gapińska and Kowal, 2009). BV is determined by the number of red cells, plasma viscosity, blood flow speed, platelet aggregation and vascular diameter.

Individuals over 60 years old have higher viscosity levels than young individuals. Ageing entails loss of water, potassium, phospholipids and adenosine triphosphate (ATP). The decrease in ATP leads to the loss of flexibility of the red cells. Additionally, the delicate brain capillaries lose their elasticity, impairing the red blood cells from entering the thinner capillaries (Bessis and Weed, 1973; Lessin et al., 1976). The association of those two factors might result in areas with lower blood irrigation, probably leading to neural death (Galduróz et al., 2007).

* Corresponding author. Address: Department of Psychobiology, Universidade Federal de São Paulo, UNIFESP, Rua Napoleão de Barros, 925, 04024-002 SP, Brazil. Tel.: + 55 11 21490168.
E-mail address: galduroz@psicobio.epm.br (J.C.F. Galduróz).

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In agreement with these findings, some studies have reported a significant decrease in regional cerebral blood flow (rCBF) with ageing and higher intensity of Alzheimer's disease. Matsuda et al. (2003) pointed to reduced cerebral blood flow in frontal cortex regions in aging subjects and showed that SPECT data reflect loss of brain volume and functional changes. The mechanisms that might lead to this reduction, however, are unknown.

The objective of the present study was to investigate whether the higher BV observed in the elderly is associated with rCBF.

2. Method

We chose to study a sample with only male volunteers in order to reduce interference factors, since there are significant differences in viscosity when both genders are compared (Galduróz et al., 2007). The subjects were divided into two groups: "young", aged 20–30 (27 volunteers), and "elderly", aged 60–70 (50 volunteers). The volunteers underwent a clinical evaluation and laboratory exams (haemogram, glycaemia, electrolytes, cholesterol, triglycerides, T_3T_4, and TSH). Subjects who presented alterations in results were excluded.

The 77 volunteers underwent single photon emission computed tomography (SPECT) on the same day that their blood was collected for BV measurements. Those evaluations were replicated eight months later, which means that our results are based on 154 data points.

2.1. Blood viscosity

Venous blood (10 ml) was collected and stabilized with 0.1% EDTA (Rand et al., 1964). Whole blood viscosity was measured within 30 min of collection with a rotational viscosimeter (Wells-Brookfield Cone/Plate Viscometer – Brookfield Engineering Labs. Inc., Soughton, MA, USA). In this technique, the resistance to rotation caused by the fluid produces a value that is proportional to the viscosity of the substance analyzed. A sample of 0.5 ml of total blood was placed in a container to which a cone-plate was coupled that kept the blood temperature at 36 °C. This system has a precision of 1% and reproducibility of 0.2%. Blood viscosity is expressed in milli Pascal (mPa).

2.2. Single photon emission computed tomography (SPECT)

Cerebral blood flow was analysed by means of SPECT. After the insertion of a peripheral venous access, all subjects remained in a supine position with their eyes open, in a quiet and dimly lit room for about 30 min. At the end of this period, 1110 MBq (30 mCi) of ^{99m}Tc-HM-PAO (Ceretec®, Amersham International) was injected. SPECT acquisition began 20 min later. Special care was taken in positioning and securing patient's heads in the head holder. The canthomeatal line was aligned perpendicularly to the horizontal plane. Images were obtained using a single-head rotating gamma camera (APEX SPX-4HR. ELSCINT) with a low-energy, high resolution, parallel-hole collimator (LEHR), energy centred at 140 keV for ^{99m}Tc, and a 20% symmetrical window. Sixty projections in a $64 \times 64 \times 16$ matrix with an imaging time of 20 s per projection were obtained. After attenuation correction, the 9-mm slices were reconstructed by back projection with a Butterworth filter. A quantitative method was used to evaluate tracer uptake. The regions of interest (ROIs) were delineated at approximately 4, 6, and 7 cm above the orbitomeatal line (OML). The cerebellar ROI was used as a reference, since there were no observations of perfusion abnormality in the cerebella of the population studied (Fig. 1). The lower the CBF was in the region evaluated, the higher the value obtained (Cerebellum – Region evaluated = Value) for each volunteer. There was only one evaluator, and she was blind to the age of the volunteer.

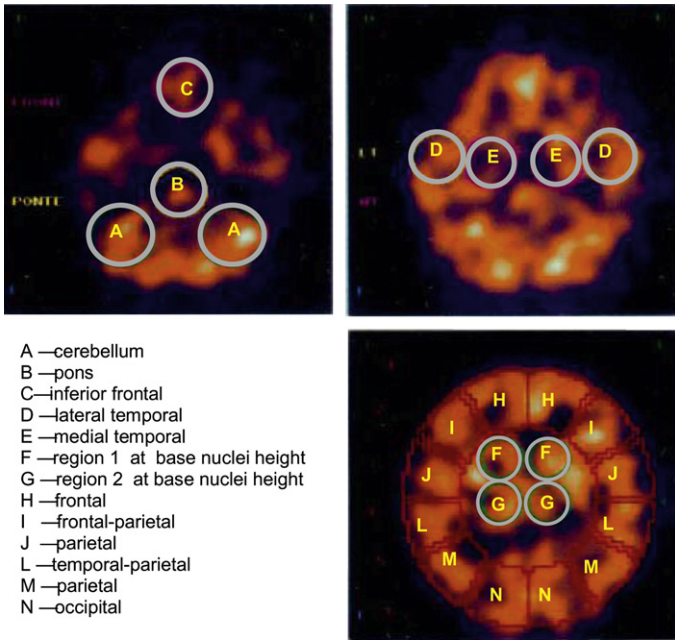

Fig. 1. Regions analyzed by single photon computerized tomography (SPECT).

2.3. Statistical analyses

The Student's *t*-test was used in the comparison of the groups' blood viscosity and cerebral blood flow. The level of significance of $p < 0.05$ was adopted for all the analyses, and the Bonferroni's Correction was used for the analyses of multiple comparisons. The Pearson's test was used in the analysis of the correlation between viscosity and cerebral blood flow. The programs used were StatPlus (version 2009) by AnalystSoft Inc. and Statistica for Windows release 5.1 F (97 edition) Copyright® 1984–1997 by StatSoft, Inc.

Table 1
Comparison between young and elderly groups with respect to regional cerebral blood flow (rCBF) in the different brain regions analysed according to the formula (Cerebellum – region evaluated = values obtained).

	Young		Elderly		*t*	*p*
	Mean	Std	Mean	Std		
Pons	42.30	5.75	38.86	6.07	1.10	0.29
Medial temporal	38.40	2.75	37.93	5.55	0.18	0.86
Lateral temporal	35.70	5.07	39.96	4.83	−1.67	0.11
Basal ganglia	25.50	4.99	23.61	4.99	0.57	0.58
Inferior frontal	49.90	5.00	50.86	9.37	−0.21	0.83
ROIs						
Left hemisphere						
Frontal	37.12	5.49	38.18	4.42	−0.92	0.36
Frontal–Parietal	34.80	5.85	36.29	4.32	−1.28	0.21
Parietal	38.85	5.63	41.83	4.16	−2.64	0.01*
Temporal–Parietal	34.61	4.45	37.46	4.21	−2.77	0.01*
Temporal	38.66	4.76	40.46	2.81	−2.09	0.04*
Occipital	30.99	4.28	31.50	3.95	−0.52	0.60
Right hemisphere						
Frontal	36.80	4.52	38.68	3.89	−1.92	0.06
Frontal–Parietal	35.74	4.44	37.56	3.75	−1.90	0.06
Parietal	39.18	4.46	43.50	3.36	−4.37	<0.0001*
Temporal–Parietal	35.28	4.08	35.77	5.55	−0.40	0.69
Temporal	39.13	2.98	40.73	3.89	−1.86	0.07
Occipital	30.31	5.11	31.83	4.09	−1.42	0.16

* Student's *t*-test for independent samples.

Table 2
Pearson's correlation between blood viscosity (BV) and regional cerebral blood flow (rCBF).

ROIs						
Viscosity total mean = 3.95 ± 0.83[†]	Pons (2)	Frontal (3)	Lateral temporal (4)	Medial temporal (5)	Basal ganglia 1 (6)	Basal ganglia 2 (7)
Total (n = 154)	0.11	−0.17	−0.26	−0.13	−0.06	0.06
Young (n = 54)	−0.04	−0.16	−0.15	−0.26	0.11	0.02
Elderly (N = 100)	0.11	−0.17	−0.26	−0.13	−0.06	0.06
1st QUARTILE (n = 67)	−0.34	0.08	0.09	−0.11	0.27	0.08
2nd QUARTILE (n = 33)	−0.16	−0.24	−0.48	−0.19	−0.23	−0.20
3rd QUARTILE (n = 38)	0.19	−0.11	0.33	−0.03	−0.18	−0.35
4th QUARTILE (n = 16)	0.23	0.32	0.59	0.70[*]	0.51	0.49
Left hemisphere	Frontal (8)	Frontal–Parietal (9)	Parietal (10)	Temporal–Parietal (11)	Temporal (12)	Occipital (13)
Total (N = 154)	−0.17	−0.10	0.05	0.01	−0.08	−0.25[*]
Young (N = 54)	0.06	0.09	−0.05	−0.02	0.04	0.02
Elderly (N = 100)	−0.17	−0.10	0.05	0.01	−0.08	−0.25
1st QUARTILE (n = 67)	0.18	0.20	0.09	0.02	0.01	0.10
2nd QUARTILE (n = 33)	−0.33	−0.43	−0.16	−0.26	−0.35	−0.05
3rd QUARTILE (n = 38)	−0.30	−0.33	−0.27	−0.11	−0.15	−0.09
4th QUARTILE (n = 16)	0.34	0.42	0.63[#]	0.88[*]	0.38	0.54
Right hemisphere	Frontal (8)	Frontal–Parietal (9)	Parietal (10)	Temporal–Parietal (11)	Temporal (12)	Occipital (13)
Total (n = 154)	−0.10	0.09	0.23	0.07	−0.02	0.01
Young (n = 54)	0.04	0.00	−0.09	−0.04	0.05	0.12
Elderly (n = 100)	−0.10	0.09	0.04	0.07	−0.02	0.01
1[O] QUARTIL (n = 67)	0.21	0.14	0.05	0.33	0.14	0.05
2[O] QUARTIL (n = 33)	−0.19	0.10	−0.27	−0.03	−0.22	−0.06
3[O] QUARTIL (n = 38)	−0.32	−0.14	−0.24	−0.07	−0.22	−0.02
4[O] QUARTIL (n = 16)	0.54	0.66	0.64	0.76	0.80[*]	0.75[*]

[*] The Bonferroni's Correction was used for the correlations, with the adjustment of values of $p < 0003$.

	Mean	S.D.
1st QUARTILE	3.15	0.18
2nd QUARTILE	3.90	0.26
3rd QUARTILE	4.71	0.24
4th QUARTILE	5.36	0.33

2.4. Ethical procedures

This research protocol was guided and approved by the Medical Ethics Commission at UNIFESP, and all volunteers signed consent forms.

3. Results

The mean age of the young volunteers (n = 27) was 25.6 ± 3.3 years, while that of the elderly ones (n = 50) was 64.8 ± 3.1 years.

The analysis of blood viscosity (BV) levels showed that the levels in the elderly group were significantly higher than those in the younger group. The mean BV of the young volunteers was 3.28 ± 0.43 mPa, and that of the elderly volunteers was 4.33 ± 0.73 mPa (t = −6.9, $p < 0.0001$). The mean number of red blood cells of young and elderly individuals did not show statistically significant differences. Comparing rCBF measures of ROIs in relation to the cerebellum, we found significant differences between the young and elderly groups in the bilateral parietal; temporal–parietal and temporal regions of the left hemisphere (Table 1).

The rCBF between hemispheres showed significant differences (Student's t-test for dependent samples, $p < 0.001$) only in the elderly group in the following regions: frontal–parietal (36.29 ± 4.32 left and 37.56 ± 3.75 on right); parietal (41.83 ± 4.16 left and 43.50 ± 3.96 on right); and temporal–parietal (37.46 ± 4.21 on left and 35.77 ± 5.55 on right), in relation to the cerebellum, indicating lower levels of perfusion in these regions.

In the analysis of all the BVs and rCBFs, independently of the age group studied (Table 2), the Pearson's correlation between BV and areas of lower rCBF showed a good negative correlation when blood viscosity was above a mean of 3.95 ± 0.83 mPa.

4. Discussion

Blood viscosity was higher in the group of elderly volunteers when compared with that of young volunteers, which is in line with previous reports (Baskurt and Meiselman, 2003; Galduróz et al., 2007). Comparing rCBF rates for the young and elderly groups, a statistically significant difference was observed in three ROIs: bilateral parietal, temporal–parietal, and temporal in the left hemisphere. This result corroborates that of Asllani et al. (2009), who separated structural decline from true CBF reduction in the elderly and showed marked CBF decreases in many brain regions. Several reports have also pointed out that cerebral perfusion decreases with age, mainly in the left hemisphere (Catafau et al., 1996; Garraux et al., 1999; Pagani et al., 2002; Herholz et al., 2002).

The great variability observed between the correlations suggests a different behavior of the ROIs in relation to rCBF, as reported in works that highlight a higher sensitivity of some areas to hypoxia conditions, as in the case of area CA1 of the hippocampus (Olson and McKeon, 2004).

Many studies point to cognitive impairment associated with hypoperfusion (Klinge et al., 2002; Ushijima et al., 2002; Kalvach and Gregova, 2005; O'Brien, 2007). Therefore, the hypothesis that the reduction in rCBF is a result of higher BV might bring interesting possibilities for the treatment/prevention of brain ageing.

Santos et al. (2003) showed that chronic use of *Ginkgo biloba* led to a decrease in blood viscosity and an increase in CBF in several regions, as well as better performance on neuropsychological tests. Other substances such as *Allium sativa* and red wine also reduce blood viscosity and might then improve cerebral blood flow. This could, in turn, lead to cognitive improvement (Jensen et al., 2006; Galduróz et al., 2007; Hou et al., 2007).

5. Conclusion

Therefore, in this study both blood viscosity and rCBF were measured at the same time in the subjects investigated, and results showed a negative relationship between blood viscosity and cerebral blood flow in certain brain areas. These findings suggest interesting possibilities for the treatment/prevention of brain ageing.

Conflict of interest

There are no conflicts of interest.

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