Age effects on the mechanical behavior of human cerebral bridging veins

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Abstract

Background. It is well established that the probability of occurrence of acute subdural hematomas in traumatic situations increases with age, since the main cause of such hematomas is the mechanical failure of cerebral blood vessels known as bridging veins. This research aims to determine whether there is an effect of age on the mechanical properties of these cerebral vessels, because previous reported studies were conflicting.

Methods. This study used mechanical tests blue of cerebral bridging veins from post-mortem human subjects. In particular, a series of in vitro tensile tests were performed on a balanced sample of bridging veins from different human subjects.

Findings. The mechanical parameters measured from the tests were analyzed by means of regression analysis looking for age related effects. The results show that there is a significant effect on both the ultimate strength, maximum stress and strain that the specimens can withstand. The quantitative analysis shows reductions of nearly 50% in ultimate stress, and almost 35% in ultimate strain.

Interpretation. Mechanical deterioration of the mechanical strength of cerebral blood vessels seems to be a major factor involved in the increase of frequency of acute subdural hematoma in elderly people in a wide range of life-threatening traumatic situations.

KEYWORDS: bridging veins, age-dependent properties, TBI, ASDH.

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Nomenclature

ASDH - Acute SubDural Hematoma

CBV(s) - Cerebral Bridging Vein(s)

CVP - Cerebral Venous Pressure

ICP - IntraCranial Pressure TBI - Traumatic Brain Injury

1 Introduction

Acute Subdural Hematoma (ASDH) is one of the most frequent types of Traumatic Brain Injury (TBI). It is mainly caused by the rupture of Cerebral Bridging Veins (CBVs) due to excessive strain and mechanical stress [1, 2, 3, 4]. Therefore, describing the mechanical behavior of CBVs is a critical issue to understand ASDH [5, 6].

On the other hand, the effect of age on brain tissue has only been occasionally studied and the results found are contradictory [7]. Some research suggests that the shear moduli increase with age during the brain development [8] while other studies suggest the opposite, at least for large strains [9, 10]. In addition, some alterations in viscoelastic properties have been reported in the literature depending on age [11].

However, if the specific mechanisms of injury and disability are considered, the importance of the age factor is clear. For example, different studies have shown that the incidence of ASDH increases with age [12, 13, 14], and it is also well known that this factor is directly associated with the rupture of the CBVs [4, 15, 16]. Although the mechanical properties of CBVs have been systematically investigated [2, 17], the literature on age-dependent effects on the mechanical behavior of CBVs is scarce, even though there is great interest in the pediatric case [18, 19] and elderly case [20].

Most studies on age effects in ASDH are based on epidemiological data and do not directly measure any mechanical property of the CBVs. A recent study, which used mechanical testing in CBVs, examined the change of rate-dependent properties in human and porcine subjects and found no significant differences with age [21]. However, it seems reasonable to assume that if the ASDH increases with age, it would be expected that this is partly due to a variation in the mechanical properties of the CBVs [2]. For this reason and due to the limited information in the literature concerning the influence of age on the CBVs, this paper re-examines the occurrence of age effects by means of uniaxial tensile tests with relaxation.

2 Data and Methods

This study was performed with human CBVs tested in a previous study, in which a constitutive model was presented and the influence of the viscoelastic contribution to the mechanical behavior was analyzed [4]. This section provides a summary of the material obtention, the tests performed and the calculations to obtain the data used in the subsequent analysis of this study.

2.1 Material and specimen preparation

For this study, different sections of the meningeal-cortex space (which included the upper part of the cerebral cortex, the meninges and the subarachnoid space) were obtained from autopsies of post-mortem human subjects (PMHS), performed by expert forensic pathologists. The study was approved by the Research Committee of the Legal Medicine and Forensic Science Institute of Catalonia (IMLCFC), where the autopsies were conducted. None of the subjects had been previously diagnosed with any blood vessel pathology.

The meningeal sections were kept refrigerated before its manipulation and preserved in airtight containers. From the meningeal sections, the CBVs were carefully dissected, and the specimens were stored at 2 °C for a maximum of 24h until tested, previously allowing them to reach room temperature for 1h.

The main dimensions of the CBVs were digitally measured from photographs taken under a stereomicroscope SMZ-168 Motic®, using the same methodology described in some previous research [4, 17], see Figure 1.

2.2 Sampling mechanism and statistical controls

For the current study, a balanced sub-sample (which prevents the occurrence of any other correlation with any other factor, as strain rate, gender, etc.) was selected (see Table 1). In particular, the correlation between age and strain rate was statistically controlled: Among all the experiments performed, a random sample was chosen in which age and strain rate were not correlated, in order to separate the effect of age and strain rate, since both can significantly affect the ultimate stress and ultimate strain [4].

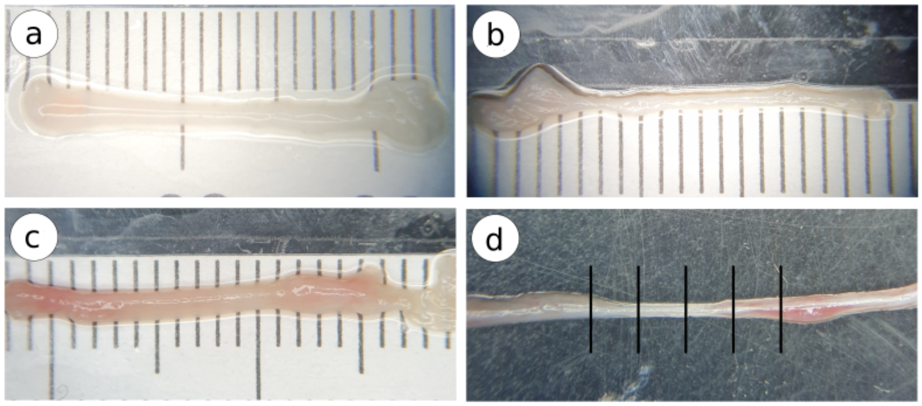


Figure 1: Four images of different CBV specimens captured with the camera coupled to the microscope (**a, b, c**). The diameter and width vary slightly along the CBV. Subfigure (**d**) shows the five measures of the apparent width in the central region.

The relative significance and potentially confounding effect of the predictor variables on the dependent variables (age, ultimate magnitudes $F_u, \sigma_u, \varepsilon_u$, Young's moduli $E_{0.10}, E_{0.15}$, and strain rate $\dot{\varepsilon}$) were investigated using linear regression models. The corresponding p-values were compared to determine the significance of the effects, for different levels of significance defined for $p \leq 0.05$.

In all cases, the homoscedasticity and independence of statistical errors were verified by means of statistical tests (Breusch–Pagan test for homoscedasticity [22, 23], Kolmogorov–Smirnov test for error independence [24]). These controls ensured that the errors were normally distributed and therefore allowed the p-value analysis to be applied to tell whether the effect of a given was significant.

2.3 Tensile testing

Each CBV was tested following the procedure described in [4]. The tensile test was performed using a Universal Test Machine (UTM) Zwick-Roell Allround-Table-Top® with a digital control unit to carefully measure displacement and the force was measured with a 20 N load cell HBM®. Special fixtures were used, which prevented slippage due to its grooved pattern surface in the inner part where it was in contact with the specimen. The position of each specimen was checked before and after the test to ensure zero slippage in all specimens. The strain rate ranged from $\dot{\varepsilon} = 0.17$ to 0.95 s^{-1} for the different CBVs.

For the computation of stress and strain, the specimens of CBV were represented as hollow cylinders of constant cross-section, made of a homogeneous and transverse isotropic material, and subjected to a uniform stress state, as in previous studies [2, 15, 16].

Figure 2(a) shows the experimental setting, and the coordinates used: the X axis coincides with the longitudinal axis, and the Y and Z axis are contained in the transversal plane. The instantaneous longitudinal stretch λ_t was computed from the measured displacement δ_t and the initial length L_0 as:

$$\lambda_t = 1 + \frac{\delta_t}{L_0} \tag{1}$$

In addition, after a length increase, the coordinates change of a material point $\boldsymbol{X}_t = (X_t, Y_t, Z_t)$ is given by:

$$x_t = X\lambda_t, \qquad y_t = Y\left[1 - \bar{\nu}_\lambda\left(\lambda_t^2 - 1\right)\right]^{1/2}, \qquad z_t = Z\left[1 - \bar{\nu}_\lambda\left(\lambda_t^2 - 1\right)\right]^{1/2} \tag{2}$$

where $\bar{\nu}_\lambda = \nu(\lambda_t)$ is the Poisson effect function that, for a linear elastic material reduces to a constant [4]. Under these considerations, the Green–Lagrange strain tensor $\mathbf{E}$, computed from the deformation gradient tensor $\mathbf{F} = \partial \boldsymbol{x}_t / \partial \boldsymbol{X}$ is determined as $\mathbf{E} = (\mathbf{F}^T\mathbf{F} - \mathbf{I})/2$ and takes the form:

$$\mathbf{E} = \frac{1}{2}\begin{bmatrix} \lambda_t^2 - 1 & 0 & 0 \\ 0 & -\bar{\nu}(\lambda_t)(\lambda_t^2 - 1) & 0 \\ 0 & 0 & -\bar{\nu}(\lambda_t)(\lambda_t^2 - 1) \end{bmatrix} \tag{3}$$

Stress is described by means of the second Piola–Kirchhoff stress tensor $\mathbf{S}$:

$$\mathbf{S} = \begin{bmatrix} \dfrac{F_t}{\lambda_t A_0} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \tag{4}$$

being F_t the instantaneous force and A_0 the initial cross-section.

The main components of both strain $\mathbf{E}$ and stress $\mathbf{S}$ tensors are the longitudinal components $E_{11} (= \varepsilon)$ and $S_{11} (= \sigma)$ respectively, whose values at each test time t generate the stress-strain curve of the test. From the stress-strain curves of the different CBV specimens, the parameters determined were the yield stress σ_y (where the curve changes from concave to convex) and the associated yield strain ε_y, the maximum stress σ_u at failure and the associated ultimate strain ε_u and the Young's Modulus E, computed as the local slope of the curve at 10% ($E_{0.10}$) and 15% ($E_{0.15}$) of strain level, so as to compare the results with the literature (see figure 2(b)).

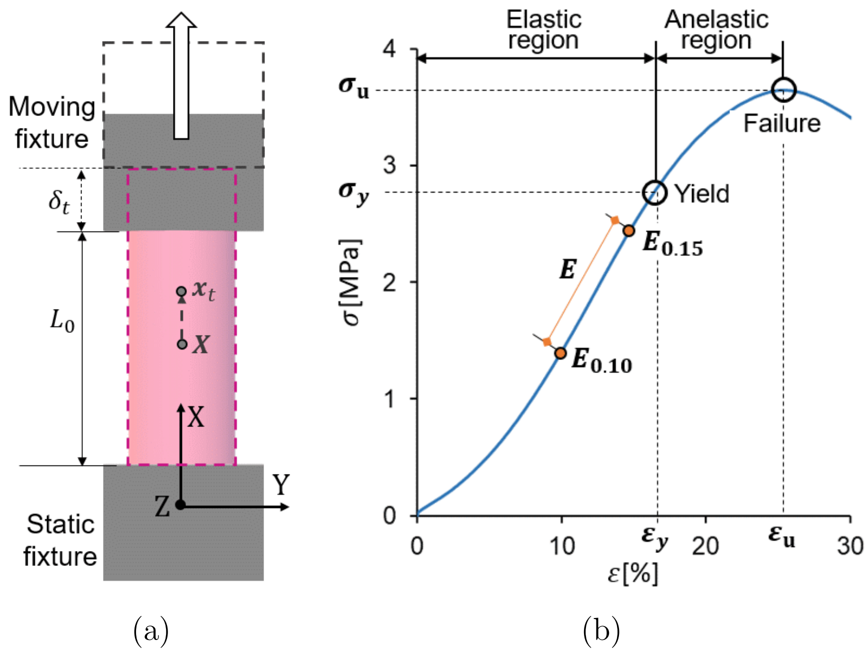


Figure 2: (a) Experimental setting scheme: The coordinate system is centered on the static fixture, with the X axis in the longitudinal direction and the Y and Z axis contained in the transverse plane. The initial length L_0 of the CBV increases after a displacement δ_t, and a point $\boldsymbol{X}$ maps to a new position $\boldsymbol{x}_t$. (b) Typical stress-strain curve of a CBV, with the main mechanical properties determined in this study.

3 Results

In this study, N = 9 human CBVs (with an average age of 67±9 years) were mechanically tested at different strain rates. The mechanical properties obtained from the tensile tests are shown in Table 1). The average values obtained for the ultimate properties were F_u = 0.684 ± 0.205 N (force), σ_u = 3.637 ± 0.975 MPa (stress) and ε_u = 0.418 ± 0.076 (strain); for the yield properties were F_y = 0.447 ± 0.127 N, σ_y = 2.380 ± 0.267 MPa and ε_y = 0.285 ± 0.038 and, finally, for the Young's Modulus values were $E_{0.10}$ = 4.639 ± 0.922 MPa and $E_{0.15}$ = 6.243 ± 0.852 MPa.

Table 1: Basic mechanical properties of the rib specimens.

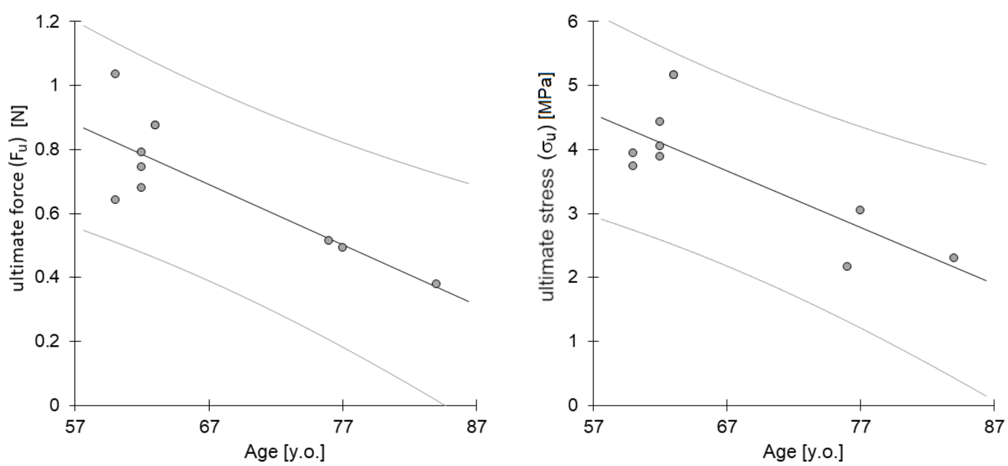
PMHS	Age [y.o.]	$E_{0.10}$ [MPa]	$E_{0.15}$ [MPa]	F_u [N]	σ_u [MPa]	ε_u [%]	$\dot{\varepsilon}$ [s^{-1}]
2627	60	4.56	6.60	1.036	3.73	42.0	0.950
2628	60	3.18	4.29	0.643	3.95	52.2	0.922
2629	62	5.03	6.51	0.791	4.44	46.9	0.723
2631	62	4.88	7.02	0.746	4.06	39.0	0.708
2633	62	5.11	6.36	0.680	3.89	37.9	0.799
2640	63	5.94	6.95	0.876	5.17	52.8	0.897
2630	76	3.66	5.60	0.513	2.17	32.8	0.566
2836	77	3.80	6.09	0.493	3.03	41.0	0.171
2632	84	5.63	6.80	0.378	2.32	31.8	0.721

The results were analyzed using regression analyses to assess a possible significant effect of age on the mechanical properties. It was previously checked that the age and the strain rate were statistically independent variables in the selected sample. This allowed to adequately differentiate between the effect of age and that produced by the strain rate.
The statistical regression analysis showed that age has a significant negative correlation with ultimate parameters. Therefore, ultimate force F_u (p = 0.005), stress σ_u (p = 0.007) (see Figure 3) and strain ε_u (p = 0.047) decrease significantly with age (see Figure 4). No significant relation was detected between age and yield properties or Young's Modulus. Table 2 shows $p-$values for linear regression in addition to Pearson's and Spearman's correlation coefficients.

Table 2: Correlations of mechanical properties with age and p-values.

Property	Pearson's r	Spearman's ρ	p−value
F_u	–0,834	–0,672	0.005 (**)
σ_u	–0,821	–0,460	0.007 (**)
ε_u	–0,528	–0,672	0.047 (*)
$E_{0.10}$	–0,009	+0,315	0.983 (NS)
$E_{0.25}$	+0,073	+0,111	0.851 (NS)

(**) highly significant, (*) significant, (NS) non-significant.



(a) (b)

Figure 3: Scatterplot of (a) ultimate force, and (b) ultimate stress (trend line and 95% confidence interval).

4 Discussion

Understanding the age effect on the mechanical properties of CBVs is an important concern to properly comprehend ASDH, even though the literature on this topic is scarce and partially inconsistent [7, 8, 9, 10]. In this study, an analysis of the effect of age on CBV mechanical properties obtained from tensile tests has been conducted. Despite the reduced sample of CBV specimens used in this study, this research allowed to find interesting results regarding the effect of age on the mechanical behavior of CBVs. The results

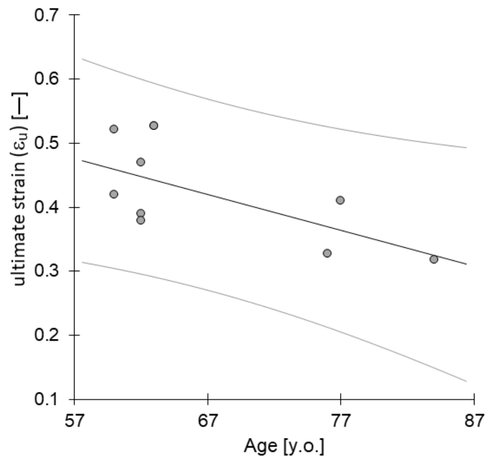


Figure 4: Scatterplot of ultimate strain (i.e., strain associated to the ultimate force, trend line and 95% confidence interval).

show that there is a deterioration in the mechanical performance of the CBVs both in stress and strain. Thus, ultimate stress ($\sigma_u, p = 0.007$) and ultimate strain decrease with age ($\varepsilon_u, p = 0.047$). This is consistent with the fact that the ASDH becomes more frequent at higher ages, being, therefore, the loss of mechanical capacity one of the factors involved in the frequency increase. While this is not surprising, this is one of the first published studies to find a clear and significant negative effect of age on the mechanical properties of CBVs. Another study that also found a significant decrease in stress σ_y with age ($\rho = 0.271, p = 0.007$) for CBVs is that of Monea et al. (2014), although they do not mention having found an effect on maximum strain [2]. These findings are consistent with other general studies that detect loss of mechanical capabilities in veins and arteries with age [25]. On the other hand, another study reported no age effects [21] in CBVs, although that may be due to both the small sample size, and the fact that they used load cycles at constant strain, so they never used strain or stress levels close to rupture, which is why age effects are surely not detectable in that type of experiment. However, the decline in mechanical properties may not be the only cause of an increased probability of ASDH. Some research has suggested that greater brain–skull relative movements are produced due to an enlarged subdural space determined by the brain atrophy [26, 27].

On the other hand, our study has not found significant changes in the stiffness of CBVs as measured by Young's modulus (as shown in Table 2).

Although other studies have pointed out that veins and, also major arteries, may experience an increase in stiffness with age [28, 29, 30], it turns out that CBVs are special because of their size and physiology, and actually the previous literature refers to other types of veins and arteries.

4.1 Limitations

Although ruptured CBVs are usually the origin of most ASDH, their growth and severity depend on other factors, such as the balance between the cerebral venous pressure (CVP) and the intracranial pressure (ICP). In fact, CVP increases along with the ICP as pressure variations occur, and the elevation of CVP as a response to the increment of ICP is thought to result from an increase in outflow resistance of the terminal portion of the bridging veins [1]. Another possible mechanism in ASDH production is presented in Zhou *et al.* (2019), where some finite element simulations showed that increased brain motion could explain the enhanced occurrence of ASDH in elderly people [31]. Even assuming that mechanical deterioration of CBVs as age increases is not the only factor affecting the frequency and severity of ASDH, it seems that aging is a major contributor to the deterioration of mechanical properties of CBVs, which in fact is related to the occurrence of ASDH (since a decrease of nearly 50% in the maximum resisted stress, and 35% in the capacity to assume strain are observed, when comparing when comparing 60-year-olds with 80-year-olds).
Another limitation of this study is that, given the nature of the specimens and their availability, the study sample is not very large. Even so, the results found are statistically clear and provide new insights in an area not previously studied. Moreover, further work is needed in order to study the influence of other factors besides age, in order to determine which are the most important factors involved in CBV deterioration and ASDH occurrence.
A final comment is that caution should be applied when extrapolating in-vitro results, as in this study, to actual in-vivo behavior. For example, Geffen and Margulis (2004) argue that brain in-vivo is a vascularized tissue, and there is a paucity of information regarding the effect of perfusion on brain mechanical properties [32]. However, this and most mechanical studies of CBVs are performed on depressurized specimens, even though some simulation studies suggest that blood pressure may have an effect on CBV rupture [33, 34, 35, 36].

5 Conclusions

This study has shown, in a small sample that there is a serious deterioration in the mechanical properties of CBVs with age, which means that both their capacity to resist stress and strain is significantly reduced. This is consistent with the reported increase of ASDH in elderly people and why they present greater vulnerability to TBI, both in traffic accidents and in other types of life-threatening traumas.
In particular, the study found clear correlations in all the ultimate mechanical properties (force F_u, stress σ_u, and strain ε_u) of CBVs, although mechanical strength is not the only factor involved in the emergence and aggravation of ASDH, it seems that it could explain partially the higher frequency of ASDH observed in elderly people.

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