Pittfalls of aneurysm sac pressure monitoring

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CHAPTER 4

Development of fibrinous thrombus analogue for in-vitro aneurysm studies

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Abstract

Objective: To develop different thrombus analogues, with mechanical properties similar to those of human fibrinous thrombus, for in-vitro aneurysm sac pressure studies.

Methods: Using Dynamic Mechanical Analysis we determined the E-modulus ($|E^*|$) at 0.8Hz, 1.0Hz, 1.5Hz and 3.9Hz of 10 different human fibrinous thrombus samples. We also determined loss and storage modulus to quantify the visco-elastic properties. For comparison, we measured the E-modulus ($|E^*|$), loss and storage modulus of gelatin, Novalyse ST8, ST14 and ST20 with and without contrast agent.

Results: Mean E-modulus of the thrombus samples (SD) at 0.8Hz, 1.0Hz, 1.5Hz and 3.9Hz was 39 (16)kPa, 37 (15)kPa, 37 (15)kPa and 38 (14)kPa, respectively. Median (SD) storage and loss modulus were 35 (12)kPa and 8 (4)kPa, respectively. Median (SD) $\tan\delta$ was 0,25 (0,06). The E-modulus of gelatin, Novalyse ST8, ST14 and ST20 was 4kPa, 27kPa, 48kPa and 60kPa, respectively. The E-modulus of Novalyse ST8, ST14 and ST20 mixed with contrast agent was 18kPa, 23kPa and 33kPa, respectively. Median (SD) storage, loss modulus and $\tan\delta$ of the 6 Novalyse samples were 30 (15)kPa, 3 (1)kPa and 0.087 (0.04), respectively.

Conclusion: All the thrombus analogues, except gelatin, had an E-modulus in the range of human fibrinous thrombi. Novalyse samples are validated thrombus analogues for in-vitro aneurysm sac pressure studies. Gelatin is not appropriate to simulate fibrinous thrombus.

4.1 Introduction

An abdominal aortic aneurysm (AAA) is a localized widening of the main artery in the abdomen (aorta). AAAs are found in 4% to 8% of elderly men and 0.5 to 1.5% of elderly women [1]. Abdominal aortic aneurysms are an increasing healthcare problem considering that the average life time increases. AAAs are usually asymptomatic, but rupture can occur, which leads to death in more than 80%. Conventionally, AAAs are repaired by interposition of a tube or bifurcated graft through large abdominal operation with cross clamping of the aorta. Elective operation carries an operative mortality of 5% [2].

Endovascular aneurysm repair (EVAR) was introduced as a less invasive alternative to conventional aneurysm surgery, since it avoids the surgical exploration of the abdomen and aortic cross-clamping [3]. During EVAR a stentgraft is placed inside the AAA through the groin. The aneurysm sac is isolated by the stentgraft from systemic pressure and blood flow. This method reduces operative mortality to less than 2% and carries a lower rate of short-term systemic complications and a shorter hospitalization [2, 4].

The Achilles heel of Endovascular Aneurysm Repair (EVAR) is the occurrence of an incomplete seal of the endovascular graft (endoleak) and a persistent pressurization of the aneurysm sac without blood flow in the sac (endotension) [5, 6]. Endoleak and endotension can still cause AAA rupture because of increased aneurysm sac pressure.

Little is known about the biomechanical environment in the aneurysm sac after EVAR. Aneurysm and stent-graft motions have been visualized to understand the complex patterns of forces in the aneurysm. Cine MRI after EVAR demonstrated increased pulsatile cranial-caudal translation of the aneurysm during the heart cycle. Anteroposterior translation of the aneurysm and pulsatile wall motion of the stent-graft were beneath the detection of cine MRI ($<$0.5mm) [7].

Many studies, in-vivo as well as in-vitro, have been undertaken to investigate aneurysm sac pressure in the presence of endoleaks and endotension. In-vitro studies give the opportunity to investigate endoleak and endotension in a controlled way. Furthermore circulation models are preferable, because these studies are less expensive, less time-consuming and, unlike for animal and clinical trials, ethical issues are avoided.

Manufacturing of life-like fusiform non-axisymmetrical AAA models has been published [8]. Validation of biomechanical properties of these aneurysm models is essential. Computer simulation demonstrated that elevated sac pressure can be caused by the complex fluid-structure interactions between luminal blood flow, endovascular graft wall, stagnant sac blood, intraluminal thrombus and aneurysm wall [9].

The human aortic thrombus can reduce the pressure on the aortic wall [10]. So thrombus should be incorporated in the aneurysm model to simulate the in-vivo

situation if pressure measurement studies are carried out. The human thrombus, which is obtained during open aneurysm surgery, can not be fitted exactly into latex aneurysm models. A thrombus analogue is needed, which is easy to mould into the aneurysm model and has the same mechanical properties after hardening.

As underlying idea for the present work, we assume that for understanding the pressure build-up on the aneurysm wall, the thrombus can be considered as behaving as a solid media as was done in several earlier publications [11, 12]. Furthermore, we will assume that the mechanical properties of thrombus is isotropic since from scanning electron microscopy (SEM) images it can be observed that no clear privileged direction exist in the material texture [13].

The pulsatile wall motion of aneurysms of 6cm is less than 0.5mm after EVAR [7, 14]. Hence, the deformation of the thrombus remains small so we expect that its material behavior can be assumed linear. This assumption will be investigated in the present study.

The Young's modulus (E-modulus), describing the elastic stiffness and the damping of the material, is the most important characteristic of the mechanical property of human fibrinous thrombus because the motion of aneurysm sac thrombus is quasi-static (heart rate: 1-2Hz) and therefore the inertia effects are assumed non-significant. Only the stiffness and maybe the viscosity are relevant in this circumstance. The aim of this study is (1) to measure the E-modulus, of human fibrinous thrombus and (2) to develop a thrombus analogue with same E-modulus as thrombus.

4.2 Methods

4.2.1 Theory of experiments

Dynamic Mechanical Analysis is a high precision technique for determination of mechanical and viscoelastic properties of materials. A Dynamic Mechanical Analyzer (DMA) runs automatically dynamic mechanical analysis, by deforming a sample under action of a pair of equal and opposite forces (F). These forces do not act along the same line of action (Figure 4.1). Points A and B move to a and b and points E and F move to e and f, respectively. The shear stress, the ratio between the external force (F) and the area of the sample ($\tau = F/A$), results in a change of sample shape. The thickness of the sample (t) is constant, so the shear stress induces a shear strain. Engineering shear strain, for small deformations, is defined as the ratio of amplitude (Δx) and thickness (t) of the sample ($\upsilon = x/t$) and thus corresponds to the small deformation angle of the sample (Figure 4.1).

The shear elastic modulus, also called the G-modulus is the ratio of shear stress to shear strain. It expresses the resistance of a material to shearing. The

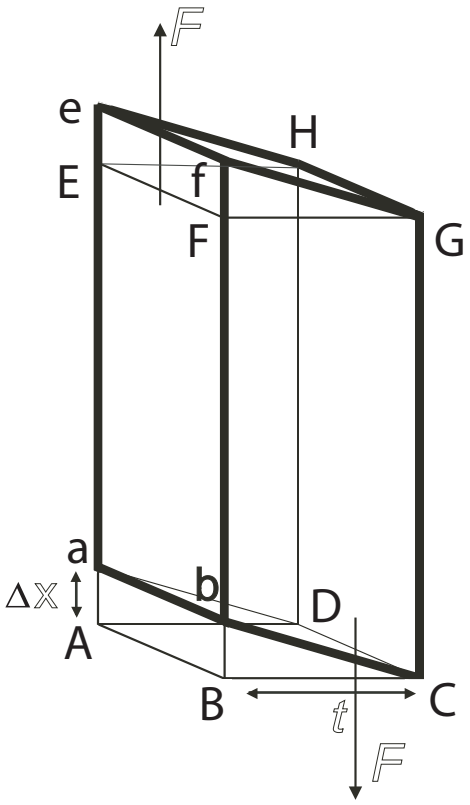

Figure 4.1: Schematic of a sample under action of a pair of equal and opposite forces (F). These forces do not act along the same line of action. Points A and B move to a en b and points E and F move to e and f. Δx is the amplitude of the sinusoidal strain (=30 μm). t is the thickness of the sample.

G-modulus is given by:

$$G = \frac{\tau}{\upsilon} = \frac{F/A}{\Delta x/t} = (F/\Delta x) \cdot (t/A) \tag{4.1}$$

The amplitude (Δx) and frequency are defined by the operator of the DMA. Amplitude and frequency are kept constant by the DMA during sample testing. The dimensions of the samples, the thickness and area, are known. The DMA calculates the stiffness of the sample ($F/\Delta x$) after measuring the external force (F). The G-modulus of the sample is calculated by multiplying the stiffness with the ratio between thickness and area (see equation (4.1)).

The E-modulus ($|E^*|$) is a measure of stiffness of a material that yields information about the deformability of the material. Although the E-modulus as well as the G-modulus is the ratio between stress to strain, the E-modulus is associated with uniaxial stress and the G-modulus with shear stress. The unit of the

G-modulus and the E-modulus is Pa. The G-modulus is related to the E-modulus through the Poisson's ratio, υ:

$$|E^*| = 2(1+\upsilon)|G| \tag{4.2}$$

The Poisson's ratio is bounded by two thermo dynamical limits; it is greater than -1 and less or equal to 0.5. The Poisson's ratio of a perfectly incompressible material is exactly 0.5.

The complex E-modulus (E^*) consists of a storage modulus (E') and a loss modulus (E'') such that when the material undergoes harmonic (sinusoidal) uniaxial deformation a stress component in phase to the displacement and another ninety degree out of phase (and thus related to the rate of deformation) exist. Hence, the material stiffness can be described by the complex modulus ($E^* = E' + iE''$), where i is the imaginary number. The magnitude of the complex E-modulus ($|E^*|$) is then defined by:

$$|E^*| = \sqrt{E'^2 + E''^2} \tag{4.3}$$

The loss modulus is related to the dissipation in the material since it is related to the part of the force proportional to the velocity. Since in bio-materials dissipation is mainly originating from viscous and porous effects, the loss modulus can be mainly related to the liquid portion of a material and the storage modulus to the solid portion. Purely elastic material has a loss modulus (E'') of 0. The storage modulus (E') of a purely viscous material is 0. $\tan\delta$ is the ratio between the loss modulus (E'') and the storage modulus (E') ($\tan\delta = E''/E'$) and is calculated by the DMA from the phase-shift between force and displacement. The storage modulus (E') and the loss modulus (E'') are calculated as follows:

$$E' = |E^*|\cos\delta \tag{4.4}$$

$$E'' = |E^*|\sin\delta \tag{4.5}$$

4.2.2 Compressibility of thrombus

Aneurysm sac thrombus was obtained during open surgery of 6 patients and thereafter frozen at -80^oC. The specimens were tested within 2 weeks. The thrombi were equilibrated to room temperature before mechanical testing. Before testing the thrombi were stored in 0.9% saline solution.

To evaluate the extent of compressibility of human fibrinous thrombus, the thrombi were pressurized in a rigid pressure box. A pressure box (10cm $\times$10cm $\times$10cm) was filled with 500ml 0.9% saline solution. The liquid level before introduction of the thrombus in the box was measured in millimeters. After introduction of the thrombus the liquid level was measured again. The volume of the thrombus before pressurization was calculated using the difference between the liquid levels

before and after introduction of the thrombus. Subsequently, the box was pressurized by inflating the box with air to 200mmHg (in-vivo the pressure in aneurysm sac will be less than 200mmHg). After pressurization, the liquid level was measured again and the volume of the thrombus was recalculated. Volume after pressurization was compared to the volume before pressurization. Compressibility of 6 thrombi was tested 3 times. With use of these compressibility experiments Poisson's ratio was estimated.

4.2.3 Test samples of Dynamic Mechanical Analysis (DMA)

Control experiments were performed to determine the effect of freezing on the visco-elastic properties of thrombus. Mechanical analysis of 3 fresh thrombus samples was performed immediately after open aneurysm surgery. The samples were frozen after mechanical testing. Subsequently, the samples were defrosted and the mechanical analysis was repeated.

As mentioned, thrombus was tested within 2 weeks after aneurysm surgery of 6 patients. Two different parts of the same thrombus, one luminal and one lateral, were tested from 4 patients because thrombi are not homogenous [15]. Only one part of the thrombi of 2 patients were tested. So 10 ($(4 \times 2) + 2$) test samples were analyzed. Other parts of these thrombi than during the compressibility experiments were used for DMA. The samples were kept wet with saline solution during experiments.

Thereafter, samples made of gelatin (Gelatin, Dr Oetker GmbH, Villach, Austria), Novalyse ST8, ST14 and ST20 (Novalyse, Kobato Nova Products BV, Ootmarsum, The Netherlands) were analyzed respectively. We analyzed gelatin and Novalyse (a polymer), because these materials are easy to mould into the aneurysm model. Novalyse consists of two liquid components, namely STA and STB. Once the components are put together in the proportion of weight 2 STA : 1 STB, Novalyse hardens in a few minutes at 20^oC.

Inhomogeneity of thrombus can be simulated by molding thrombus analogues with different mechanical properties in one aneurysm model. These different analogues could be visualized with fluoroscopy if one analogue contains contrast agent. Therefore, the mechanical properties of thrombus analogues with contrast agent were determined as well. Novalyse ST8, ST14 and ST20 were mixed with the contrast agent Télébrix 350 (Télébrix 350 ,Guerbet Nederland BV, Gorinchem, The Netherlands) at a volume ratio of 15 :1. These samples were named Novalyse ST8C, ST14C and ST20C, respectively.

All test samples were cut in parallelepipeds and were glued to two sheets of glass (18×18mm) (Colle seconde lijm, Bison International, Goes, The Netherlands).The thickness of the samples (t) was measured by a digital millimeter sliding caliper in two decimals. The samples used had a thickness comprised between 2.5mm and 4.0mm. The area (A) of the samples was calculated from the size of

the sheets of glass.

4.2.4 Dynamic Mechanical Analysis

The Dynamic Mechanical Analysis of the samples was performed by a Dynamic Mechanical Analyzer (DMA) (DMA Q800, TA, New Castle Delaware, USA) (Figure 4.2).

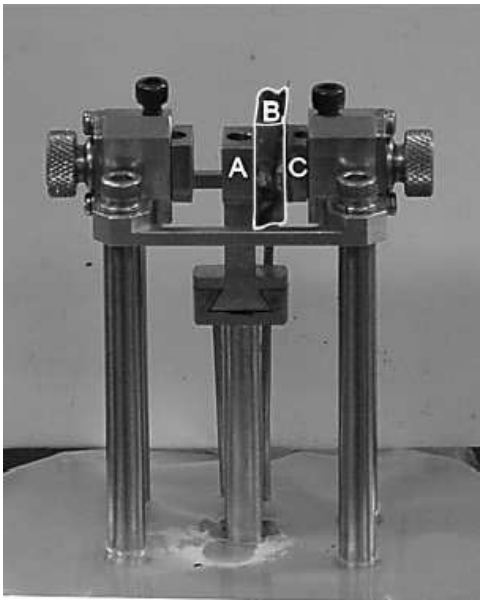

Figure 4.2: Experimental set-up of the Dynamic Mechanical Analyzer (DMA). One shaft (A) moves and the other shaft (C) does not move, so a sinusoidal strain is generated to the thrombus samples (B).

As already mentioned, the DMA measures the mechanical properties of the samples by submitting the samples to sinusoidal shear strain. During this study the DMA applied 4 excitation cycles before actually measuring. Hence we can assume that the bio-material is properly preconditioned before measurements were taken.

The frequency of sinusoidal shear strain was adjusted to 0.8Hz, 1Hz, 1.5Hz and 3.9Hz respectively. This corresponds with a heart rate between 48 and 234 beats per minute. The frequency of 0.8Hz, 1 Hz and 1.5Hz were considered as the most important ones, because these represent the physiological heart rate. The amplitude (Δx) was adjusted to 30μm. A small amplitude was chosen, because DMA has to be nondestructive to the test sample and in order to ensure that the deformation of the sample remains small (deformation angle $\Delta x/t = 30\mu\text{m}/3\text{mm}$ of the order of 0.01). Furthermore, this deformation is of the same order of magnitude as the deformation expected for thrombus in vivo. Indeed the pulsatile wall

motion of aneurysms, with a median diameter of 55mm, is during post-operative follow-up between 0.25 and 0.52mm.[14] So the ratio between motion and diameter is about 0.45%, which can be taken as an estimate of the order of magnitude of the deformation in vivo. The deformation in our shear tests was of the order of 1% as indicated above.

Mechanical properties of 3 thrombi were determined with a deformation of 30μm as well with a deformation of $60\mu m$. By comparing the results measured at 30μm with those measured at 60μm we were able to confirm our assumption, that the material behavior of thrombus is linear.

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The mechanical property of the human fibrinous thrombi was determined by calculating the E-modulus magnitude ($|E^*|$) after measuring the stiffness of the samples. Furthermore, the visco-elastic property of the thrombus samples was expressed by calculating the storage and the loss modulus. Subsequently, the E-moduli magnitudes ($|E^*|$), the storage and loss modulus of the thrombus analogues were determined.

4.3 Results

Compressibility of the thrombi was tested 3 times. No difference existed between the first, second and third measurement. The volumes of the thrombi did not change after pressurization, so human fibrinous thrombus can be assumed incompressible and the Poisson's ratio of human fibrinous thrombus must by close to 0.5. Using this Poisson's ratio, the G-modulus of human fibrinous thrombus is related to the E-modulus through the following equation:

$$E^* = 2(1 + 0.5)G = 3G \tag{4.6}$$

Control experiments demonstrated that the visco-elastic properties of thrombus do not change after freezing since the test results after freezing were identical to those before freezing. The mechanical properties of the 3 thrombi did not change during experiments after increasing the displacement from 30μm to 60μm. Hence our assumption, that the material behavior of thrombus is linear during small deformations, proved to be correct.

Figure 4.3 depicts the E-moduli magnitudes ($|E^*|$) of the 10 thrombus samples. The mean E-modulus (SD) at 0.8Hz, 1.0Hz, 1.5Hz and 3.9Hz was 39 (16)kPa, 37 (15)kPa, 37 (15)kPa and 38 (14)kPa, respectively.

As mentioned above, two different parts, one luminal and one lateral, of the same thrombus from 4 patients were tested. The E-modulus ($|E^*|$) of the luminal

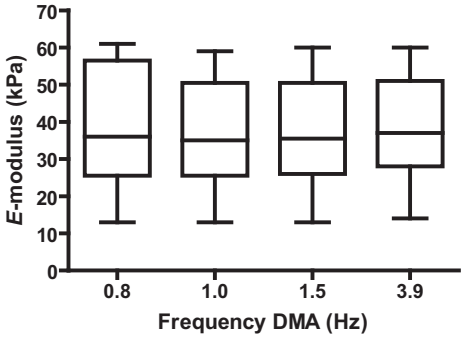

Figure 4.3: Boxplot of the E-moduli magnitudes ($|E^*|$) of 10 fibrinous thrombus samples of 6 different patients, which were obtained during open surgery. Median, 25-th, 75-th percentiles and the range are shown.

part was in all thrombi lower than that of the lateral part. The median (SD) E-modulus of the luminal part at 0.8Hz, 1.0Hz and 1.5Hz was 30 (18)kPa, 31 (15)kPa and 31 (16) kPa, respectively. The median (SD) E-modulus of the lateral part at these frequencies was 42 (15)kPa, 41 (14)kPa and 41 (15)kPa, respectively.

The storage (E') and loss (E'') modulus of the 10 thrombus samples are depicted in Figure 4.4. The storage modulus, the loss modulus and $\tan\delta$ did not change at 0.8Hz, 1.0Hz and 1.5Hz. The median (SD) storage modulus and the median (SD) loss modulus were 35 (12)kPa and 8 (4)kPa, respectively. The median (SD) tanδ was 0,25 (0,06). The high standard deviation values of the E-moduli ($|E^*|$), the storage (E') moduli and the loss (E'') moduli indicate that these moduli differ substantially from patient to patient.

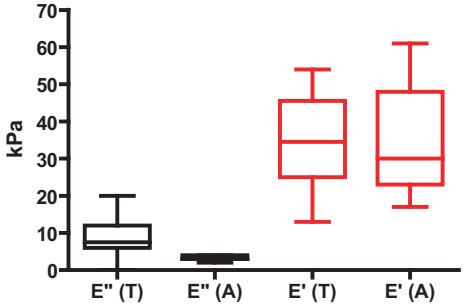

Figure 4.4: Boxplot of the loss (E'') and storage (E') modulus of 10 fibrinous thrombus samples (T) and of 6 thrombus analogues (A). Median, 25-th, 75-th percentiles and the range are shown.

The E-moduli ($|E^*|$) of the thrombus analogues are given in Table 4.1. Only the E-modulus of gelatin was out of the range of the E-moduli of the tested human fibrinous thrombus. The storage (E') and loss (E'') modulus of the 6 Novalyse

samples are depicted in Figure 4.4. The storage modulus, the loss modulus and $\tan\delta$ were similar at 0.8Hz, 1.0Hz , 1.5Hz and 3.9Hz. The median (SD) storage modulus and the median (SD) loss modulus were 30 (15)kPa and 3 (1)kPa, respectively. The median (SD) tanδ was 0.087 (0.04). The E-modulus of Novalyse without contrast agent was greater than the E-modulus of Novalyse with contrast agent. The storage modulus decreased in particular by adding contrast agent. Therefore, $\tan\delta$ increased after mixing Novalyse with contrast agent (Table 4.1).

Table 4.1: E-moduli ($|E^*|$) of different thrombus analogues

Sample	**Frequency of DMA (Hz)**	E**-modulus (kPa)**	$\tan\delta$
Gelatin	0.8	4	4.18E-02
	1.0	4	4.05E-02
	1.5	4	3.84E-02
	3.9	4	2.67E-02
Novalyse ST8	0.8	27	7.04E-02
	1.0	27	7.11E-02
	1.5	27	7.44E-02
	3.9	26	5.72E-02
Novalyse ST8C	0.8	18	1.56E-01
	1.0	18	1.59E-01
	1.5	19	1.58E-01
	3.9	17	2,07E-01
Novalyse ST14	0.8	48	7.27E-02
	1.0	48	7.22E-02
	1.5	48	7.34E-02
	3.9	49	7.29E-02
Novalyse ST14C	0.8	23	1.33E-01
	1.0	23	1.36E-01
	1.5	23	1.42E-01
	3.9	23	1.46E-01
Novalyse ST20	0.8	60	6.84E-02
	1.0	60	6.89E-02
	1.5	60	6.96E-02
	3.9	61	6.96E-02
Novalyse ST 20C	0.8	33	9.95E-02
	1.0	33	1.03E-01
	1.5	33	1.07E-01
	3.9	33	1.01E-01

Novalyse ST8C, ST14C, ST20C are with contrast agent

4.4 Discussion

The aim of this study was to characterize human thrombus, obtained from aortic aneurysms, and to develop thrombus analogues with an E-modulus similar to human fibrinous thrombus. The Poisson's ratio of human fibrinous thrombus was found to be very close to 0.5, as expected for many biological materials [16]. This is in line with the assumptions used in several earlier publications [9, 12], where it was assumed that υ was 0.45 and 0.49, respectively. The Poisson's ratio of Novalyse is also 0.5 (specifications Kobato Nova Products BV).

This study demonstrates that human fibrinous aneurysm sac thrombus has visco-elastic properties. The ratio between loss modulus and storage modulus was found to be lower than 25% for the thrombus indicating that deformation rate plays non-negligible role. Nevertheless, since we are interested in defining a thrombus analogue having quasi-static properties of the same order of magnitude of real thrombus, the viscosity contribution is considered as secondary.

As its name suspects, visco-elastic material consists of a viscous and an elastic network. The elasticity of a material expresses its ability to restore energy and the viscosity expresses its ability to dissipate energy. Identifying and reproducing the proper visco-elastic stiffness of the thrombus is essential since, together with the shape of the aneurysm and the stiffness of the wall, it plays a primordial role in determining the aneurysm wall stress and the pressure distribution within the aneurysm sac [10, 17] These data of the visco-elastic properties of human fibrinous thrombi are also useful for computer simulation of aneurysms.

Our results of mechanical properties of human fibrinous thrombus are comparable to the results of other studies. Di Martino et al. determined in 21 thrombus samples, obtained from 6 patients, the E-modulus. The range of variability for the specimens was 50-200kPa [11] Wang et al. carried out tensile testing on 50 thrombus specimens [13] After linearization of their constitutive model, an $E-$modulus of about 50kPa was found. Di Martino et al. as well as Wang et al. performed uni-axial mechanical tests, whereas we performed dynamic shear stress tests. In our opinion shear stress tests are more appropriate to determine the mechanical properties of human fibrinous thrombus. Indeed thrombus is a soft tissue that can be obtained in practice only as thin layer and therefore it is very difficult to properly control the test parameters in uni-axial testing. This can be understood by observing that the shape of the sample cut out of a thrombus in the study by Di Martino et al. only vaguely resembles the standardized shape for material sample [11] In addition ensuring a proper clamping of an uni-axial soft sample is a major difficulty. On the contrary the shear test methodology used here is well suited for identifying the properties of soft materials, because it is more controllable than uni-axial tests.

All the thrombus analogues tested in this study, except gelatin, had an E -modulus magnitude in the physiologic range of E-moduli magnitudes of human

fibrinous thrombi. This range, from 13 to 59kPa, was determined in this study by controlled experiments with human thrombus. The $E-$modulus magnitude of gelatin is only 4kPa. The loss modulus of the thrombus analogues were however smaller than the loss modulus of thrombus. For instance $\tan\delta$ of the Novalyse analogues was measured between 7% and 20% (see Table 4.1) whereas $\tan\delta$ is around 25% for a thrombus. Hence the viscosity of the analogues is clearly smaller than the viscosity of the thrombus although of the same order of magnitude. Since the viscosity effect is not dominant in a thrombus, the fact that the analogue viscosity is not equivalent is not considered as a serious drawback when using Novalyse as thrombus analogues. Therefore Novalyse could be considered as a bio-mimetic alternative for human fibrinous thrombus.

To our knowledge this is the first study in which mechanical properties of human fibrinous thrombus are measured to develop a validated thrombus analogue for in-vitro aneurysm sac pressure studies. Gelatin is used as a thrombus analogue in previous in-vitro studies [18, 19] The mechanical property of gelatin was not determined in these studies. We determined in this study that the E-modulus of gelatin is much lower than that of human fibrinous thrombus, so gelatin seems to be not appropriate to simulate fibrinous thrombus. However, we can not exclude that the $E-$modulus of gelatin is comparable to fresh thrombus.

In a recent in-vitro study dough was used to mimic the aneurysm thrombus [20] The authors described that dough had similar pressure transmission properties that were measured and equilibrated with the human sac thrombus by using a standard calibration process. They did not publish the data of their calibration process. Therefore, the results can not be compared with the present study. Furthermore, it is not clear if they are able to simulate thrombus with different mechanical properties. This is necessary, because we demonstrated that thrombi of different patients do not have identical mechanical properties.

In conclusion, we developed thrombus analogues to simulate different human fibrinous thrombi. The mechanical properties of the analogues were similar to the mechanical properties of human thrombi. The thrombus analogues are easy to handle and fit exactly in latex aneurysm models. Inhomogeneity of human thrombi can be simulated by molding analogues with different $E-$moduli in the same aneurysm model. Using these analogues it will be possible to perform validated in-vitro aneurysm sac pressure studies in future.

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