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Chapter 9

BIOLOGICAL ADHESIVES

José María García Páez and Eduardo Jorge-Herrero

Unidad de Biomateriales, Servicio de Cirugía Experimental, H.U. Clínica Puerta de Hierro, c/San Martín de Porres 2; 28035 Madrid, Spain

9.1 Introduction

The need to effectively manage very important problems like hemostasis and tissue sealing has had a strong influence on the development of modern surgical techniques. A group of chemical products (natural and synthetic materials) known as sealants, glues, or tissue adhesives has been developed to reduce bleeding and promote tissue sealing. For example, it has been shown that the use of a cyanoacrylate adhesive contains the bleeding from gastric varices with a higher rate of success and a lower rate of mortality than the administration of ethanolamine oleate, a sclerosing agent [1]. In blepharoplasty, an eye surgery technique, octyl-2-cyanoacrylate, a cyanoacrylate approved by the U.S. Food and Drug Administration (FDA) has been used with excellent results in terms of quality when compared with the use of sutures [2]. Three types of adhesives have been utilized in cardiovascular surgery: fibrin glues, which are resorbable but do not provide strong adhesion and require rapid healing of the tissue; enbucrilates, which have been used successfully for left ventricular free wall rupture [3] but produce a marked exothermic reaction and are unstable; and biological glues. The latter have been employed to bond pericardial patches and reinforce sutures. In aortic dissection, a very serious clinical situation, a bioadhesive is used to bond the proximal and the distal edges of the dissected aorta, which are then sutured. The mechanical behavior of the bioadhesive in this clinical situation has yet to be characterized and the association of sutures appears to be indispensable [4].

Chemically, tissue glues and adhesives can be defined as any substance with characteristics that allow for polymerization [1]. This chemical polymerization

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must also hold tissues together. Glues and adhesives are materials whose attachment to a surface principally involves molecular attraction.

Certain logical features are required of surgical glues. First of all, the chemical substance employed as the adhesive must remain present and preserve its chemical characteristics long enough for the tissues to bond well without any additional supports and for the necessary time. Evidently, a rapid degradation of the adhesive before the healing process is completed would be counterproductive. The degradation of the adhesive should always occur after that time. Some authors describe the mechanism of action of a good adhesive as a result of two different physical forces. The glue is usually spread on each of two objects; it is held to them by adhesion involving intermolecular forces between the two dissimilar materials. With an effective glue, adhesion and cohesion are about as strong as the internal cohesion of the objects to be joined.

Finally, it must be safe. The agent should not create more problems than it solves. When first introduced, fibrin sealants were banned from use in the United States because of the risk of the transmission of infections. Not until blood products could be adequately screened for these pathogens were they approved. Safety is a critical issue. Like all biomaterials, adhesives should meet certain safety norms, which are regulated by different international organizations. Adhesives and glues must promote tissue healing without the risk of infection or viral transmission. To obtain these properties, the different manufacturers must test their products at least for acute, subacute, local, and systemic toxicity according to well-established protocols that recommend that the tests be carried out in each individual component, in the final product (if there are two or more components mixed together to obtain the final glue or adhesive) and in its degradation products.

As these materials will act in living organisms, it is necessary to take into account that the human body is a very aggressive environment. It is a saline medium with a temperature of 37 °C, so certain conditions—minimum tissue toxicity at the application sites, parallel sealing and biodegradability times to get a proper healing time, wettability; ease of utilization in the surgical theater, and of course, low cost—must be met.

At the present time, tissue adhesives are being used in a number of surgical specialties, but all of them have to offer the same properties or qualities. They must be easy to use (as mentioned above), have fast action in bleeding systems, undergo no exothermic reaction during polymerization, have sufficient strength for each type of tissue to which they are applied and produce no inflammatory reactions.

We review some of the general characteristics of these adhesives and describe our experience (in experimental models) in the mechanical behavior of biological glues that could potentially be utilized, alone or in combination with sutures, to join inert biological tissues that have been chemically treated. The

biological tissue employed was glutaraldehyde-fixed calf pericardium similar to that employed in the manufacture of the valve leaflets of cardiac bioprostheses.

9.2 Fibrin glues

Fibrin glues are employed in surgery to help bond tissues during wound healing and repair. Carless et al. [7] published a systematic review of the randomized controlled trials carried out to study the efficiency of fibrin sealants in 2002. Being resorbable, their use in implants or bioprostheses is prohibited.

9.2.1 Composition

A commercially prepared fibrin sealant comes in a kit that includes two lyophilized components. One component contains a pooled fibrinogen factor XIII concentrate, which is dissolved in an antifibrinolytic solution (aprotinin). The other component is bovine thrombin reconstituted with 40 mM $CaCl_2$. The kit also includes a double-barreled syringe system that releases equal volumes of fibrinogen and thrombin through a needle. Historically, the main problem with fibrin sealants was the high associated risk of hepatitis transmission from the human plasma pooled to obtain fibrinogen. The composition of commercial solutions varies considerably. The fibrinogen concentration ranges between 50 and 115 mg/mL, whereas that of factor XIII is 5–80 IU/mL. The thrombin concentration ranges from 200 to 600 u/mL[2].

9.2.2 Mechanism of action

Fibrin sealants are employed for tissue healing and topical hemostasis, so their action mimics the blood coagulation cascade (Figure 9.1) to obtain a final semirigid, insoluble, fibrin clot by mixing the two components. Thrombin catalyzes the step that transforms fibrinogen into fibrin monomers and, with calcium ions as a cofactor, activates factor XIII. Fibrin then starts to polymerize by means of electrostatic interactions and hydrogen bonds. In the presence of calcium, active factor XIIIa converts non-covalent bonds to covalent bonds, which render the cross-linked structure of a fibrin clot.

The fibrin clot is degraded by physiological fibrinolysis. The antifibrinolytic agent, aprotinin, supplied in the kit slows the breakdown of the clot by plasmin, the fibrinolytic agent of our organism.

To prevent virus transmission, fibrin sealants are subjected to a variety of chemical treatments to ensure a safe product, free from virus. At present, fibrinogen can be obtained from individual units of blood plasma that are previously tested for the associated risk of hepatitis and human immune deficiency virus (HIV). In addition, for viral inactivation, commercial solutions are purified

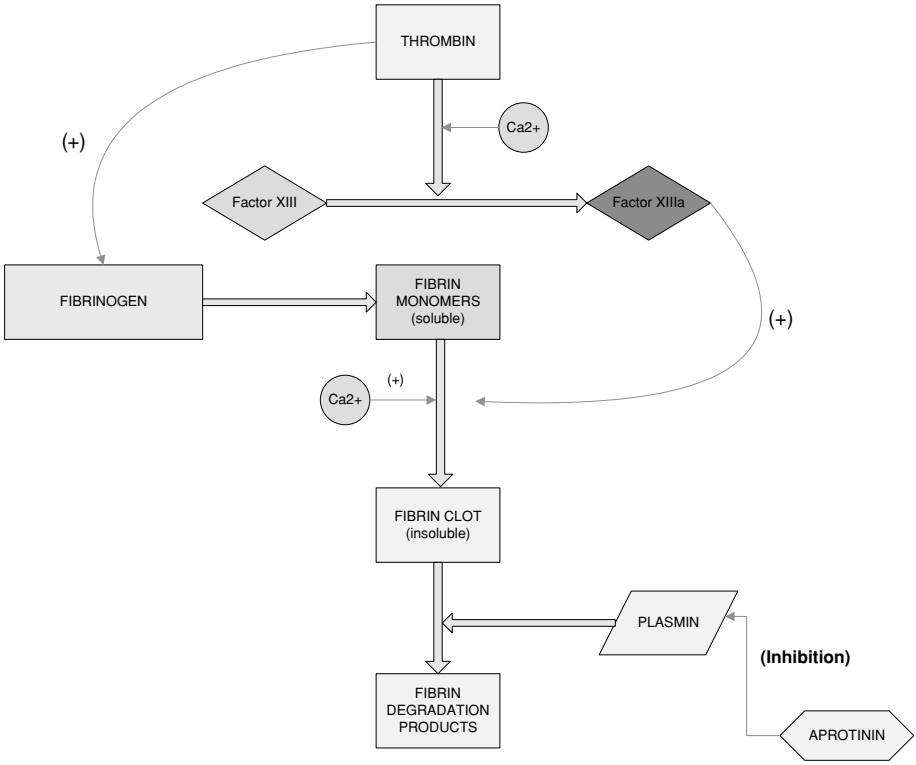


Figure 9.1. Mechanism of clotting factor interactions

using a two-step vapor-heating method at 60 and 80 °C, or other methods such as pasteurization (10 h in an aqueous solution at 60 °C), detergent treatments, nanofiltration, chromatography, ultraviolet C light, etc. A combination of these treatments is preferable because none of them is 100% effective. The methods employed by the manufacturers offer a sufficient margin of safety against HIV and hepatitis B and C viruses. In 2000, Gosalbez et al. reported a parvovirus B19 transmission attributed to the use of fibrin sealant [3], but there are no cases of serious viral transmission reported in the literature.

9.2.3 Mechanical behavior

A study of the behavior of fibrin sealants when employed in combination with conventional sutures showed no improvement in the resistance or elasticity of biological tissue samples. However, a more homogeneous mechanical behavior was observed in sutured samples in which a fibrin glue was subsequently applied to the holes created by the suture. These results do not have a clear explanation and further studies will be required to confirm or refute their validity [10].

Table 9.1. Mean tensile stresses at the time of rupture of the samples

Series	No.	Mean (Mpa)	Standard deviation	95% Confidence interval
PPI	12	6.83	2.34	5.35, 8.32
PI	12	7.06	2.43	5.52, 8.61
PC	12	10.40	2.66	8.72, 12.10
PD	12	8.27	3.18	6.24, 10.29
PPD	12	8.70	2.71	6.98, 10.41

PPI: samples from the left side of the pericardial sac, sutured at a 45° angle and glued. PI: pericardium from the left side, sutured at a 45° angle. PC: control pericardium. PD: pericardium from the right side, sutured at a 90° angle. PPD: pericardium from the right side, sutured at a 90° angle and glued.
PC versus PI: $p = 0.027$; PC versus PPI: $p = 0.016$.

9.2.4 Mechanical characteristics

For the study of the mechanical characteristics of these adhesives, we analyzed a commercially available fibrin glue, Tissucol® Immuno 5.0, that is authorized for medical use. This sealant is manufactured from two components of human origin: a lyophilized protein concentrate to be dissolved in a solution containing aprotinin and lyophilized human thrombin, which is reconstituted with a calcium chloride solution (Baxter AG, Vienna, Austria).

The study consisted of subjecting 60 samples of calf pericardium, a material that is utilized in the manufacture of bioprosthetic valve leaflets, to tensile testing. A running suture from edge to edge, at a 45° (PI) or 90° (PD) angle with respect to the principal axis, using 5.0 Prolene was performed in 24 samples. Another 24 samples (PPI and PPD) were sewn in the same manner, after which the holes made by the suture were reinforced with the fibrin glue. Twelve samples were neither sutured nor glued to serve as a control group (PC). All the samples were then subjected to tensile testing until rupture and the mean tensile stresses being exerted at that point were compared. These stresses, expressed in MPa, are shown in Table 9.1.

In the control series (PC), the mean value was 10.40 MPa. In the sutured and glued series, the mean values ranged between 6.83 and 8.70 MPa. Statistically significant differences were observed only when series PC was compared with the series sutured at a 45° angle (PI) ($p = 0.027$) and that sewn at a 45° angle and glued ($p = 0.016$).

9.2.5 Study of the elongation (strain)

The stress in MPa was analyzed for an elongation, or deformation, of 15%. The findings are shown in Table 9.2. In the control series (PC), the mean value was 3.15 MPa, which was significantly different when compared with the mean value in the other series, which ranged between 0.92 and 1.98 MPa ($p = 0.001$ to $p = 0.0041$).

Table 9.2. Tensile stress in MPa for an elongation of 15%

Series	No.	MPa	Standard deviation	95% Confidence interval
PPI	12	1.81	1.05	1.14, 2.47
PI	12	1.98	0.93	1.38, 2.57
PC	12	3.15	1.29	2.33, 3.97
PD	12	1.55	1.00	0.91, 2.18
PPD	12	0.92	0.53	0.59, 1.26

PC versus PPI: $p = 0.013$; PC versus PI: $p = 0.041$; PC versus PD: $p = 0.002$; PC versus PPD: $p = 0.001$.

The results obtained confirm the loss of resistance to tensile stress in the samples sutured from edge to edge, regardless of the angle of the suture line, when subjected to this 15% elongation.

This does not imply that the sutured and the glued series (PPI and PPD) present greater elasticity, although their behavior is seen to be more uniform, as shown by linear regression analysis comparing the tensile stress in the control series with that of the other series (Table 9.3).

The homogeneity of the samples, and thus of the results, is of the utmost importance for predicting the durability and safety of devices made with biomaterials.

In conclusion, fibrin glues add little to the resistance or elasticity of the samples, although their contribution to the homogeneity of the samples, if confirmed, should be taken into account.

9.3 Biological glues

Gelatin–resorcinol–formaldehyde blue (GRF): This glue (also known as French Blue) was developed in the 1960s by Cooper and Falb [11] as an alternative to the cyanoacrylates. The mixture of gelatin and resorcinol (3:1) and addition of an 18% formaldehyde solution renders a sealant which cross-links tissues (covalently and avidly) in less than 1 min.

Table 9.3. Linear regression coefficients, where PC represents the independent variable (x), and PPI, PI, PD, and PPD are dependent variables (y)

Series	a_1	a_2	r
PPI (y)	0.542	0.018	0.996
PI (y)	0.586	0.031	1.000
PD (y)	0.542	0.018	0.999
PPD (y)	0.542	0.018	0.999

r: correlation coefficient.

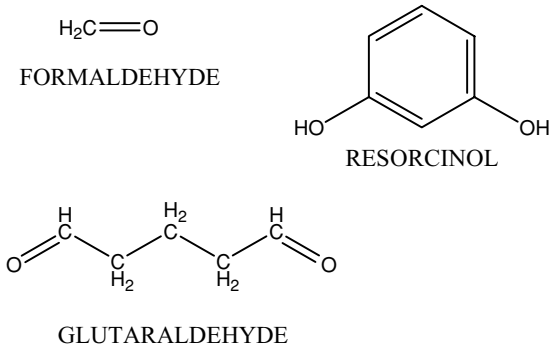


Figure 9.2. Chemical structure of the components of some BioGlues

BioGlue: Evolved from GRF glue, it is composed of 10% glutaraldehyde and 45% bovine albumin. When these two components are combined, the aldehyde groups of glutaraldehyde form stable imine cross-links with the amino groups of the proteins (Figure 9.2). The polymerization of the adhesive commences immediately and the reaction is completed in less than 2 min.

Both GRF and BioGlue have been used in a variety of soft tissue applications, but technical problems and the cytotoxicity of formaldehyde and glutaraldehyde have limited their application to acute type A aortic dissection.

The use of and results with these sealants are controversial. Some authors, in a retrospective 20-year analysis, report the use of GRF as extremely useful during initial emergency surgery for acute type A dissection, making the procedure much easier and safer [12]. Others who have reviewed its use report alterations of the aortic wall, unacceptable long-term complications and a high incidence of recurrent aortic regurgitation [4, 12, 13]. Still others prefer full root replacement to treat dissection of the aortic root [15]. These controversial data should be considered with caution. Success with biomaterials of this type (as with other types of surgical procedures or pharmacological treatments) depends on the experience of the surgical team, the amount of the product applied, and the physical conditions of the tissue, which is to be sealed. In other words, the correct use of the glue and previous training on the part of the surgeon (if inexperienced) in *in vivo* models prior to employing it in patients are essential aspects.

9.3.1 Mechanical characteristics

We compared the mechanical behavior of two commercially available adhesives, the biological glue "BioGlue" and the cyanoacrylate Loctite 4011, as bonding agents in 18 samples of a biological tissue, calf pericardium, which were cut in half and then glued with a 1 cm^2 overlap [16]. The major objective

Table 9.4. Results after tensile testing until rupture in samples glued with Loctite 4011 with BioGlue

Series	No.	Mpa	SD	95% CI	kg	SD	95% CI
Loctite	12	0.15*	0.05	0.12, 0.18	1.56**	0.49	1.25, 1.88
BioGlue	6	0.04*	0.01	0.02, 0.05	0.41**	0.15	0.25, 0.57

SD: standard deviation. 95% CI: 95% confidence interval.
*$p = 0.001$.
**$p = 0.001$.

of this assay was to determine the mechanical resistance to tensile testing of the samples after being rejoined. The mean tensile stresses at rupture are shown in Table 9.4. They are expressed in MPa and machine kg (the load to which the samples were being subjected at rupture according to the tensile testing machine) for a better comparison.

In both cases, the samples repaired with the biological glue showed a statistically significant loss of resistance when compared with the samples bonded with the cyanoacrylate ($p = 0.001$).

Perhaps the greatest problem with the biological glue is that, in order for it to be effective and achieve the necessary resistance, it has to be applied over a dry surface, a difficult condition to meet in this assay in which the calf pericardium was treated with glutaraldehyde at the time of gluing. It would appear to be equally difficult to achieve a dry surgical field for the repair of aortic dissection [4].

9.3.2 Study of the strain (elongation)

To assess the elongation that the samples underwent, we determined the mathematical fit of the values for stress (y) and strain (x) in the two series. The best fit corresponded to a third-order polynomial, the shape of which is expressed as $y = a_1x + a_2x^2 + a_3x^3$. The coefficients of the resulting curves appear in Table 9.5.

Table 9.5. Coefficients of the stress–elongation (strain) curves, showing the mechanical behaviors of the series glued with Loctite 4011 and with BioGlue

Series	a_1	a_2	a_3	R^2
Loctite	−0.07	4.22	−8.03	0.861
BioGlue	−0.02	0.98	−1.09	0.919

$y = a_1x + a_2x^2 + a_3x^3$, where y is the stress in MPa and x the per unit elongation.
R^2: coefficient of determination.

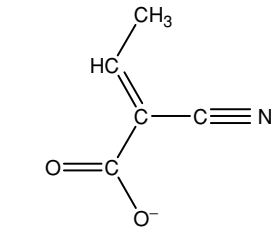
The analysis of these functions shows that both adhesives allow a marked elongation of the samples, approximately 20%, at very low levels of stress: 0.1 MPa for the tissue glued with the cyanoacrylate and 0.04 MPa for that repaired with the biological glue.

9.4 Cyanoacrylate adhesives

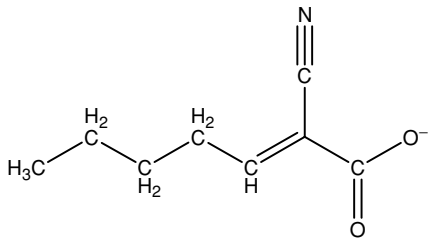
Cyanoacrylate tissue adhesives are pale yellow or transparent liquid monomers that polymerize rapidly through an anionic mechanism in the presence of weak bases such as water, alcohol, or amino groups (from proteins) that come in contact with the tissue surfaces. It is an exothermic reaction that yields a strong flexible film that bonds the wound edges.

Methylcyanoacrylate was the first material tested but was ruled out because of its rapid *in vivo* degradation. Longer-chain alkylcyanoacrylates (Figure 9.3) such as *n*-butyl cyanoacrylate and octylcyanoacrylate were developed to avoid this problem. Butyl cyanoacrylates have poor tensile strength, a circumstance that limits their use to small lacerations and incisions. The development of a longer-chain (octylcyanoacrylate) improved the performance of these biomaterials as adhesives for wound repair.

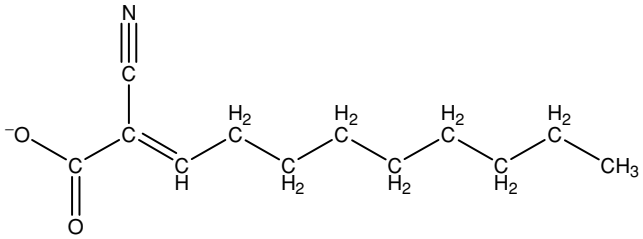
Cyanoacrylates in contact with living tissues in a moist environment polymerize rapidly to create a thin elastic film of high tensile resistance which



METHYLCYANOACRYLATE



n-BUTYLCYANOACRYLATE



OCTYLCYANOACRYLATE

Figure 9.3. Cyanoacrylates used in biological glues

guarantees firm adherence, stronger than that obtained with fibrin glues. Cyanoacrylates provide a flexible, water-resistant coating that is not impaired by blood or organic fluids and that also inhibits microbial growth. Easy to apply, these adhesives do not require the use of local anesthetics. The polymerization time varies as a function of the type of tissue with which the glue comes in contact and the nature of the fluids present. Polymerization starts after 1–2 s and takes about 1–1.5 min. Some authors prefer the superior physical properties of octylcyanoacrylate compared with butyl cyanoacrylate to repair facial lacerations [17]. As advantages, cyanoacrylates slough off spontaneously within 5–10 days, eliminating the need for suture removal.

Thus, it can be said that they are more cost-effective than sutures or staples because of the reduced need for follow-up and practitioner time [17–19].

Some disadvantages of the cyanoacrylates are the decreased tensile strength and the requirement that the areas to be treated be dry. Moreover, the application of an excessive amount of product, in addition to prolonging setting time, increases the exothermal reaction associated with polymerization, with possible thermal damage to the tissue. Thus, the glue should never be applied inside a wound over mucous membranes. It should also be avoided over areas of frequent friction, such as hands or feet, because of the risk of detachment of the adhesive.

Singer and Thode reviewed the literature on octylcyanoacrylates and reported that the current generation of octylcyanoacrylates (high-viscosity formulations) can be used successfully in a wide variety of clinical and surgical settings for multiple types of wounds involving most of the surface of the human body [20]. In an experimental study in rats, using another formulation, ethyl-2-cyanoacrylate, the histopathological analysis of vascular, myocardial, and pulmonary tissue sections demonstrated that there were no significant differences between sutures and ethyl-2-cyanoacrylate in controlling hemorrhage and air leakage [21].

9.4.1 Mechanical characteristics

We assessed the mechanical characteristics and stability over time of a commercially available cyanoacrylate, Glubran 2 (*n*-butyl 2-cyanoacrylate (monomer)/methacryloxysulfolane (monomer) (GEM, s.r.l., Italy). It is a transparent, instantaneous biological adhesive with low viscosity that is authorized for medical use according to the VSP norm (class VI). *(footnote) The results of the study are currently pending publication.

9.4.2 Resistance to rupture

Samples of calf pericardium, cut from the pericardial sac in two perpendicular directions, longitudinally, or from root to apex, or transversely, were subjected to tensile testing.

The pericardium had previously been treated for 24 h with 0.625% glutaraldehyde (pH 7.4) prepared from a commercially available solution of 25% glutaraldehyde (Merck) at a ratio of 1/50 (w/v), in 0.1 M sodium phosphate buffer. Then 60 samples, 30 cut in longitudinal direction (series LP) and 30 cut transversely (series TP), were cut in half and glued with Glubran 2, with an overlap of 0.5 cm (for a total surface area of 1 cm^2). Twelve additional samples, 6 longitudinal (series LC) and 6 transverse (series TC), were used as controls.

The samples were stored until the assay at 4 °C in saline (0.9% NaCl) plus two antibiotics: streptomycin at a concentration of 333 μg/mL and penicillin at a concentration of 2000 U/mL. Six samples each from series LP and TP were subjected to uniaxial tensile testing, always in the direction of the principal axis of the sample, until rupture 7, 30, 60, 90, and 120 days after being glued. The controls were assayed on day 7. The trials were performed on an Instron TTG4 tensile tester (Instron Ltd., High Wycombe, Buck, U.K.), which determines tensile stress and the elongation, or strain, it produces.

The mean results at rupture in kilogram, according to the load being exerted by the machine at that moment, are shown in Tables 9.6 and 9.7. While Table 9.6 shows a statistically significant loss of resistance in the glued samples when compared with the controls on day 7, Table 9.7 demonstrates that the results in the glued samples assayed up to and on day 120 do not change significantly, indicating the stability of the bond.

9.4.3 Elastic behavior

We have observed no loss of elasticity over the 120-day period that could be attributed to a hardening of the tissue secondary to the use of the adhesive. On day 120, the elastic behavior of the glued samples was maintained or even improved, a circumstance that suggests that there are no deleterious effects in this respect over time.

The analysis of the deformation, or elongation, of the samples was of most interest in the series assayed 120 days after being glued (Table 9.8). We observed a reversible deformation after rupture, that is, once the region affected by the

Table 9.6. Comparison of the means in the control series (LC and TC) and the glued series (LP and TP) cut longitudinally and transversely, respectively, on day 7 after gluing

Series	No.	Mean (kg)	Standard deviation	95% Confidence interval	*p*
LC	6	13.35	2.71	10.51, 15.19	*
TC	6	12.24	3.67	8.38, 16.09	**
LP	6	1.56	0.54	0.99, 2.12	*
TP	6	1.87	0.34	1.50, 2.23	**

*LC versus LP: $p = 0.001$.
**TC versus TP: $p = 0.001$.

Table 9.7. Comparison of the means in the glued series (LP and TP) cut longitudinally and transversely, respectively, on days 30, 60, 90, and 120 after gluing

Series	No.	Mean (kg)	Standard deviation	95% Confidence interval
Day 30				
LP	6	1.28	0.51	0.73, 1.81
TP	6	1.10	0.66	0.41, 1.79
Day 60				
LP	6	1.04	0.23	0.79, 1.29
TP	6	1.18	0.56	0.59, 1.77
Day 90				
LP	6	1.55	0.63	0.88, 2.22
TP	6	1.10	0.89	0.17, 2.03
Day 120				
LP	6	1.67	0.62	1.02, 2.32
TP	6	1.39	0.54	0.83, 1.96

rupture had amply surpassed the elastic limit [22]. To explain this phenomenon, it is necessary to take into account the differences in the elastic behaviors of the various regions of a given sample, with loads concentrated in the area near the glued portion. The collagen fibers of that zone would absorb these loads, undergoing permanent deformation and rupture, while the collagen fibers farther from the repair would be subjected to less stress, not surpassing the elastic limit. Once the load was eliminated, they would recover their original length [23].

Finally, we wish to point out that this method of bonding using cyanoacrylates demonstrates considerable resistance, but probably not sufficient for their use without other bonding elements in bioprostheses or implants. However, it allows a surprising degree of elasticity in tissue samples subjected to tensile testing.

Table 9.8. Percentages of elongation, or deformation, in series cut longitudinally (LP) and transversely (TP) 120 days after being glued

Elongation	No.	Mean (%)	Standard deviation	95% Confidence interval
Irreversible				
LP	6	10.13	7.95	1.78, 18.47
TP	6	8.55	9.49	1.42, 18.51
Reversible				
LP	6	14.51	7.41	6.73, 22.28
TP	6	12.43	5.86	6.27, 18.58
Total				
LP	6	23.89	3.48	20.24, 27.55
TP	6	20.97	4.23	16.53, 25.41

We obtained similar results, with stable resistance to tensile stress for up to 150 days and marked elasticity of the bond, with Loctite 4011, a commercially available ethyl cyanoacrylate described above [24], which is also authorized for medical use according to the VSP norm (class VI).

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