Therapeutic Embolization by Cyanoacrylate Liquid Glues Mixed with Oil Contrast Agent: Time Evolution of the Liquid Emboli

Yongjiang Li, Dominique Barthes-Biesel, and Anne-Virginie Salsac

Abstract

Glue embolization is a minimally invasive treatment used to block the blood flow to specific targeted sites. Cyanoacrylate liquid glues, mixed with radiopaque iodized oil, have been widely used for vascular embolization owing to their low viscosity, rapid polymerization rate, good penetration ability and low tissue toxicity. In this study, we have conducted an in vitro study to quantitatively investigate the polymerization kinetics of two n-butyl cyanoacrylate (nBCA) glues (Glubran 2 and Histoacryl) mixed with an iodized oil (Lipiodol) at various concentrations. The polymerization process of the glue-oil mixture is systematically characterized upon contact with a protein ionic solution mimicking plasma and compared to the case without protein. The results provide essential information for interventional radiologists to help them understand the glue behavior upon injection, and thus control embolization.

Keywords

Glue embolization • Cyanoacrylate glue • Polymerization kinetics

1 Introduction

Glue embolization is a therapeutic treatment technique used to block the blood flow to specific targeted sites. It is carried out under X-ray by introducing an embolic glue, mixed with a radiopaque iodized oil, into the circulation through a microcatheter. The technique can be performed as a definitive treatment or an adjunct to the management of arterio-venous malformations, tumors, trauma or hemorrhage [1, 2]. Cyanoacrylate liquid glues are widely used as embolic agents owing to their low viscosity, rapid polymerization rate and low tissue toxicity. Histoacryl (B. Braun, Melsungen, Germany), a pure n-butyl cyanoacrylate (nBCA) glue, has been the only glue available for external use in Europe for many years, but it is still not approved for intravascular use by the European Community (EC). It has, nevertheless, been tested for more than 10 years on patients [3]. One commonly used liquid adhesive that has the EC approval for endovascular use is Glubran 2 (GEM, Viareggio, Italy), which consists of nBCA mixed with metacryloxysulpholane (MS) as comonomer. The addition of MS allows to lower the polymerization temperature to about 45 °C and to thus reduce cytotoxicity [4]. Upon injection in the blood flow, a glue-oil mixture simultaneously polymerizes and flows with blood, leading to vessel occlusion. However, the procedure is difficult to control, because very little information exists on the polymerization kinetics of the glue-oil mixture. One empirical technique consists of dropping a small quantity of glue-oil mixture onto a plasma substrate and visualising its change in opacity [5]. This procedure provides empirical information on the initial stage of polymerization inside a thin sheet of glue mixture, only. We have designed a novel experimental setup to characterize precisely the polymerization kinetics inside a glue-oil mixture upon contact with an ionic solution containing (or not) protein concentrations similar to blood. The objective of the study is to use this technique to analyze and compare the polymerization process of Glubran 2 and Histoacryl, mixed with a radiopaque oil (Lipiodol, Guerbet, Aulnay-sous-Bois, France) at various concentrations, and identify the influence of proteins on it.

2 Materials and Methods

Glubran 2-Lipiodol (G-L) and Histoacryl-Lipiodol (H-L) mixtures are prepared at glue concentrations $C_G = 100\%$, 50% and 25% by means of a female luer connector attached

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to two 1-ml syringes, one loaded with glue and the other with Lipiodol. The mixing process consists of passing the content back and forth, from one syringe to the other at high speed. Two model solutions are used as substitutes of human blood plasma: an ionic solution (IS) consisting of PBS with 0.08% glucose and a protein solution consisting of PBS mixed with bovine serum albumin (BSA) at concentrations 80 g/L (8%) or 40 g/L (4%). The two latter solutions are referred to as IS-BSA8 and IS-BSA4, respectively.

The polymerization reaction is studied under static conditions in a vertical glass capillary tube (internal diameter $D_t = 1.06 \pm 0.01$ mm) by following the procedure described by Li et al. [6, 7]. The lower end of the tube, filled with the glue-oil mixture to be tested, is put in contact with the reacting solution (IS or IS-BSA): this creates a sharp, well-defined interface between the two liquids. As the polymerization proceeds, the glue mixture density increases, which leads to an increase of opacity. This change in opacity of the fluids is monitored with an imaging system consisting of a high-speed camera (SA3, Photron, USA) coupled to a back illumination source (Schott-Fostec, LLC, USA) (Fig. 1a). An upwards vertical z-axis is defined along the tube with origin $z = 0$ at the bottom of the capillary tube: the progression of the polymerization reaction is then evaluated from the change in image grey level $G_p(t, z)$ of the glue mixture at measuring points equally distributed along the z-axis with an interval $0.5D_e$, where D_e is the diameter of the liquid region measured on the image. Grey levels are averaged within boxes of width $0.7D_e$ and height $0.4D_e$ centered on each test point. The progression of the polymerization reaction is monitored with two recording phases: a continuous recording to capture the beginning of the polymerization process at a frame rate of 50 fps over 217.8 s or 435.7 s, followed by a time-lapse mode to monitor the long-term polymerization process at a frame rate of 0.5 fps. The duration of the time-lapse mode ranges from 60 to 240 min depending on the glue concentration.

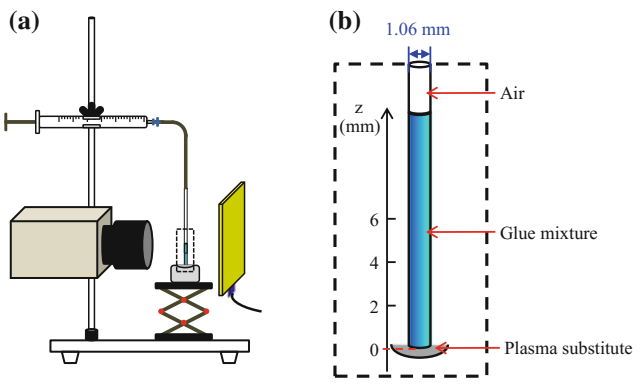

Fig. 1 **a** Experimental setup to study the polymerization of glue-oil mixtures on contact with a reacting solution: a camera monitors the changes in grey level of a glue sample contained in the tube and lighted from behind. **b** Detail of the capillary tube and of the coordinate system

3 Results and Discussions

3.1 Polymerization Phases

A typical polymerization process of a G-L mixture (C_G = 50%) on contact with a protein solution (8%) is shown in Fig. 2a. As soon as the two liquids are in contact, a darkening appears at the tube bottom indicating the polymerization of the mixture. The darkening front propagates upwards and stops at a distance z_f at time t_f, thus creating a polymerized glue plug. In the case shown in Fig. 2a, $z_f = 2.1 \pm 0.3$ mm for $t_f = 90 \pm 60$ s: the polymerization process is thus fast. Scanning electron microscope (SEM) observations of the bottom surface of the polymerized glue plug show a complex network of connected polymerized structures with interstices filled with oil. Qualitatively, the resulting structure is hard and resists compression. Some thirty five minutes after the first polymerization has stopped, a second polymerization phase takes place. The polymerization front propagates upwards from the upper boundary of the glue plug and reaches the top of the mixture column after $\sim$1 h from the moment of contact (Fig. 2a). The final grey level is much lighter than the one in the plug, indicating that the new polymerized bulk is less opaque and thus less dense than the plug. SEM images of a section of the polymerized column show micro oil droplets encapsulated by polymerized glue. Qualitatively, the column is still a hard solid that resists compression, like the plug. Similar phenomena are observed for a 50% H-L mixture, as shown in Fig. 2b. Note that in this case the top of the Histoacryl plug is not as sharp as that of Glubran 2: the corresponding plug height is $z_f = 2.9 \pm 0.3$ mm for a time $t_f = 245 \pm 60$ s. In conclusion, the polymerization reaction proceeds in two different phases which are referred to as slow and fast volumetric polymerization, respectively, and which are discussed in the following.

3.2 Polymerization Reactions and Kinetics

A careful analysis of the evolution of the grey level $G_p(z, t)$, as described in detail in [7], allows us to evaluate z_f and t_f. Fast polymerization results are shown for a variety of conditions in Fig. 3a. Since the polymerization process is random, there is some scatter of the results. As expected, t_f increases with z_f. For the 50% G-L mixture, the fast polymerization altogether propagates over an average distance $z_f = 2.1 \pm 0.4$ mm over an average time $t_f = 132 \pm 73$ s,

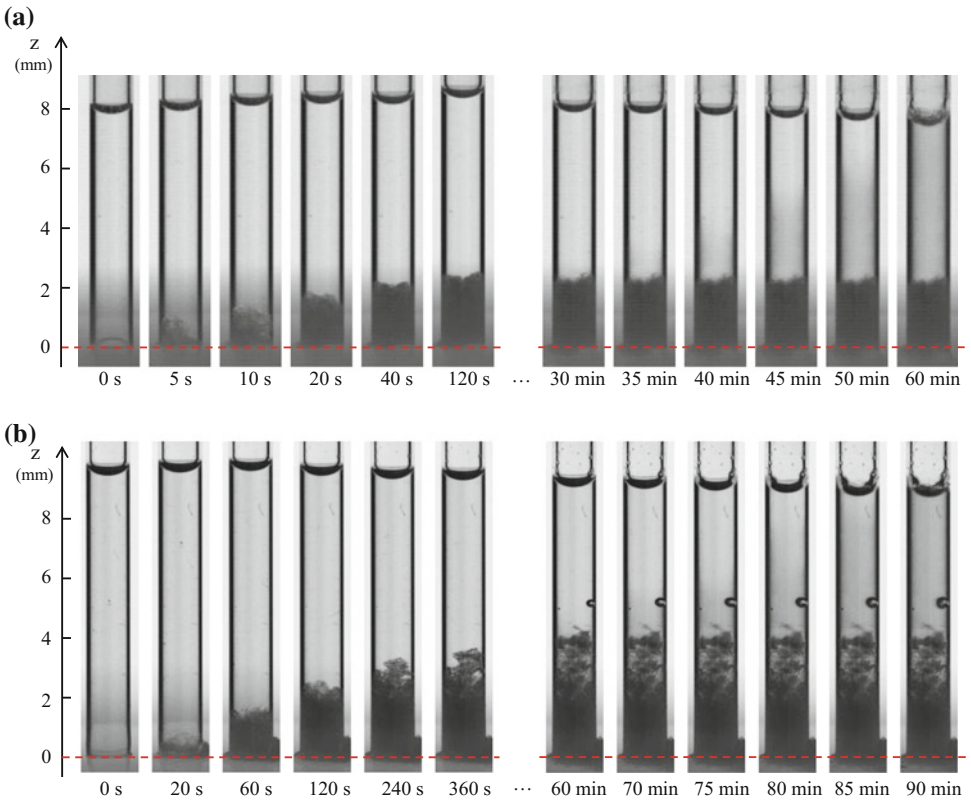

Fig. 2 At time $t = 0$, a glue-oil mixture (C_G = 50%) is put in contact with IS-BSA8. The darkening of the glue solution indicates that polymerization is occurring. A fast polymerization reaction over the two first minutes is followed by a slow polymerization some 30 min later. **a** G-L mixture; **b** H-L mixture

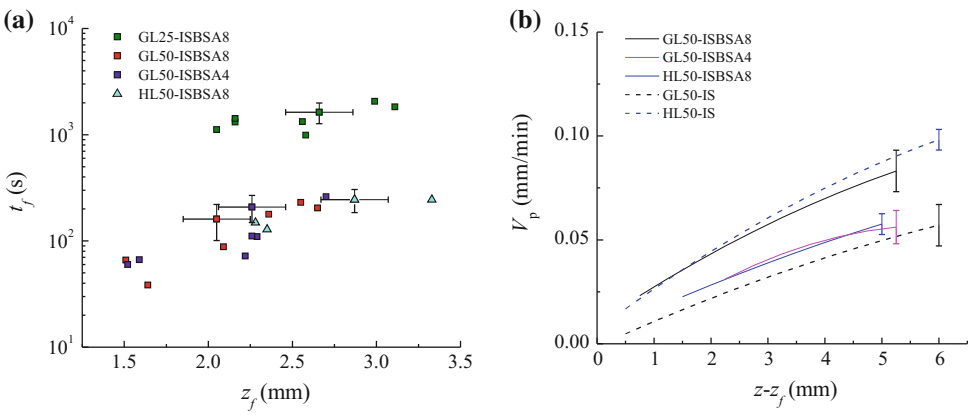

Fig. 3 **a** Time t_f necessary to polymerize a distance z_f during the fast polymerization. **b** Average front propagation velocity V_p during the slow polymerization for various mixtures upon contact with different protein solutions

leading to an average propagation velocity $z_f/t_f \sim 0.95$ mm/min. We note that there are no significant differences between 4 and 8% BSA concentrations, which means that there is a saturation of BSA molecules. However, when C_G is reduced to 25%, t_f increases significantly to about 20 min, and the average propagation velocity reduces to $z_f/t_f \sim$ 0.11 mm/min, which is an order of magnitude slower than for 50% mixtures. Histoacryl tends to create slightly larger plugs $z_f = 2.7 \pm 0.5$ mm, but the difference with Glubran 2 is not significant (Fig. 3a).

The second phase of polymerization is slow enough to allow us to measure the propagation velocity V_p of the reaction front [7]. As shown in Fig. 3b, V_p increases with z, because the reaction is exothermic. For all cases of glue-oil mixtures on contact with protein solutions, V_p varies between 0.02 and 0.08 mm/min, which is much smaller than z_f/t_f. The values and tendencies of V_p are comparable with those obtained for glue-oil mixtures on contact with pure IS (Fig. 3b). It should be pointed out that no slow polymerization phase is observed for a 25% G-L mixture on contact with either IS-BSA8 or IS. For pure Glubran 2 or Histoacryl polymerizing with IS-BSA8, both fast and slow polymerization reactions are observed. However, the fast phase is very quick and extends over a short distance $(z_f \sim 1$ mm,

$t_f \sim 5$ s), which makes it difficult to measure it with a good precision. In addition, the slow phase velocity is very difficult to assess from the image grey levels. Nevertheless, a glue column of 5 mm in height, completely polymerizes within 10 min.

The fast polymerization is triggered by the BSA molecules which have about 583 side chains of amino acids, and thus many possible sites for a zwitterionic polymerization [8, 9]. It is fast because the concentration of BSA molecules is high and thus provides a large number of potential initiation sites. This results in the formation of star polymeric structures, branching out from one BSA molecule [10], which would explain the compact structure of the fast reaction plug at the bottom of the tube. When the fast polymerization stops, the glue mixture above the plug still contains non-polymerized monomers. The slow polymerization is probably triggered by charges on the surface of the polymer in the plug. These charges lead to an anionic polymerization, similar to what is observed when the glue is put in contact with a pure ionic solution. The polymer structure is then composed of linear chains of monomers and is then less dense than the structure resulting from the zwitterionic polymerization. Increasing the oil concentration leads to an increase of the mean distance between the monomer molecules and thus of the chain formation time, as observed empirically [5]. The two tested nBCA glues differ only by the addition of the co-monomer metacryloxysulpholane (MS) to Glubran 2. The addition of MS does not modify significantly the polymerization phases and kinetics. It leads however, to a dispersion of results which is quite larger for Glubran 2 than for Histoacryl, as can be surmised from the relative size of the error bars in Fig. 3b.

4 Conclusions

The experimental setup we designed allows us to make a detailed analysis of the polymerization process when an nBCA glue, mixed with a radiopaque oil, is put in contact with a protein solution analogous to blood plasma. It thus allows to monitor what happens inside the bulk of a glue volume, when it is injected into blood. The main findings are that (i) the polymerization proceeds on two steps: a fast zwitterionic reaction leading to the formation of compact structures over a couple of minutes, is followed by a slow anionic reaction leading to less compact structures over tens of minutes; (ii) the addition of a radiopaque oil, which is necessary for intravascular applications, has a major effect on the reaction kinetics: the higher the oil concentration, the slower the polymerization; (iii) there is no significant difference between Histoacryl and Glubran 2, as regards to the polymerization kinetics. The typical time that it takes for Histoacryl and Glubran 2 to polymerize over a 1-mm thickness varies from 5 s for pure glue to about 1 min for a 50% glue concentration, and 10 min for a 25% glue mixture. Such information can help interventional radiologists understand the glue behavior upon injection, and thus control embolization.

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Conflict of Interest The authors declare that they have no conflict of interest.

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