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Effect of Glacial Acetic Acid and Ethiodized Oil Concentration on Embolization with n-Butyl 2-Cyanoacrylate: An in Vivo Investigation

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BACKGROUND AND PURPOSE: Precise control of the polymerization dynamics of cyanoacrylate mixtures used in the embolization of cerebral arteriovenous malformations is required to achieve a safe and permanent obliteration of the lesion. In this study, in vivo embolization using mixtures of Histoacryl, Lipiodol Ultra-Fluid, and glacial acetic acid (GAA) was investigated. The present study investigated whether increased ethiodized oil concentration or the addition of GAA increased rate of embolization.

METHODS: Using embolic mixtures containing Histoacryl (N-butyl 2-cyanoacrylate [NBCA]), the embolization process in the femoral and subclavian arteries of the rabbit was examined. Various embolic agents composed of ethiodized oil and N-BCA mixtures, either with or without the addition of minute quantities of GAA, were injected. Blood flow through the aforementioned arteries was measured during embolization. The transient decay of blood flow to zero was modeled, and an optimized model parameter, termed the time elapsed to flow arrest (TEFA) factor, was compared with the experimental data related to the embolization process.

RESULTS: The TEFA factor was independent of the variation of the ethiodized oil concentration in the mixture ($P > .05$). In contradistinction, the addition of GAA significantly increased the TEFA factor ($P < .05$). Moreover, a linear relation between the TEFA factor and the quantity of GAA in the mixture was discerned.

CONCLUSION: Predictable control of the embolization process with N-BCA in vivo is attained by varying the amount of GAA in the embolic mixture.

A cerebral arteriovenous malformation (AVM) is a congenital lesion of the brain that shunts blood flow through a network of diseased vessels, therein bypassing normal cerebrovascular beds. The annual rate of intracranial hemorrhage resulting from AVM rupture is 2% to 4% per year, with each bleed having a mortality rate of 10% to 15% and a morbidity rate of

$<50\%$ (1–5). It is estimated that the prevalence of AVMs is 0.1% (4, 6).

A minimally invasive treatment modality that has assumed an important role in the concert of AVM therapy is embolization. Embolization is curative in 5.6% to 20% of embolotherapy cases and serves as an adjunct treatment to surgery or radiosurgery in the remaining cases (7–13). N-butyl 2-cyanoacrylate (NBCA) is a fast acting liquid adhesive polymer that has become the preferred embolic medium for the embolization of AVMs (9, 11, 14–18). The polymer chain is initiated with contact of the anions present in blood as NBCA is injected into the feeding arteries of the lesion (19). It is frequently mixed with an ethiodized oil, such as Lipiodol, which imparts radiopacity to the embolic mixture. Moreover, it has been proposed that ethiodized oil increases the polymerization time of NBCA by reducing the contact of blood with the monomer (9, 20). Furthermore, glacial acetic acid (GAA) may be added to the oil-NBCA mixture in microliter quantities (to oil-NBCA volumes of >1 mL) to further delay the polymerization. The induced delay of the polymerization process by the addition of GAA is thought to be achieved by transient neutral-
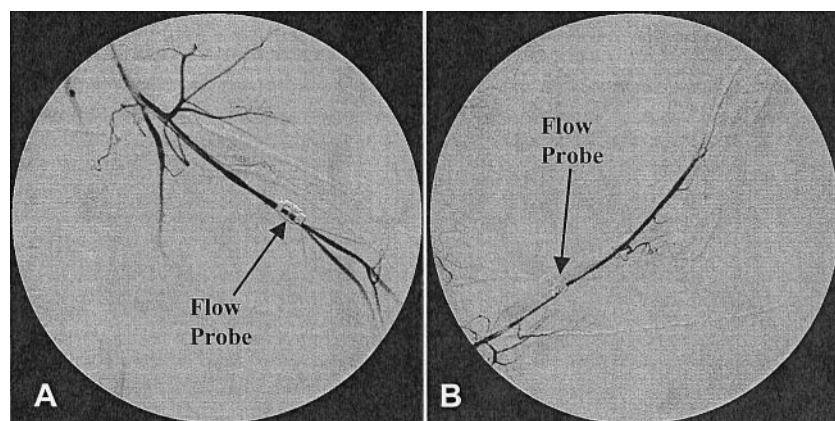
Fig 1. Digital subtraction angiograms show rabbit arteries with flow probe positions indicated (*arrows*).
A, Femoral artery.
B, Subclavian artery.

ization of the weakly basic blood environment and premature termination of the polymer chain (21).

Control of the polymerization kinetics of NBCA is essential to permanently obliterate the lesion without untoward sequelae. Repermeation of AVMs embolized with NBCA mixtures has occurred as a result of failure to obtain complete and solid casting of the arteriovenous transition (9, 22). It has been reported that total nidal penetration of NBCA to the draining veins produces permanent AVM occlusion (12). However, penetration of the embolic agent into the draining veins may lead to complications, including hemorrhage and pulmonary emboli (23–26).

Previously, the polymerization times of NBCA mixed with Lipiodol or Pantopaque was measured by placing droplets of the mixtures on tilted cover glasses contaminated with citrated human blood (27). Polymerization time was considered to be the amount of time elapsed from the contact of the liquid adhesive mixture to the glass until the onset of polymerization, as measured with a stopwatch. It was found that by increasing the concentration of the contrast agent (Lipiodol or Pantopaque), the polymerization time of the mixtures increased.

Spiegel et al (21) recorded the polymerization times of mixtures containing a cyanoacrylate mixed with iophendylate oil and various quantities of GAA by injecting the embolic mixture into a steady flow rig made of transparent plastic tubing. An observer with a stopwatch measured the time from injection until a visual change occurred in the embolic mixture. The results indicated that increases in the amount of GAA added to the mixture of isobutyl-2 cyanoacrylate and iophendylate oil increased the time required for this visual change to occur.

Brothers et al (20) compared the polymerization times of isobutyl-2 cyanoacrylate and NBCA mixed with both GAA and iophendylate oil. The embolic mixtures were dropped onto transparent syringe caps containing human plasma. The syringe caps were imprinted with newsprint size lettering, and the polymerization time was defined as the time elapsed from the contact of the embolic mixture with the plasma until the lettering became illegible, as determined by an observer with a stopwatch. The results of this investigation indicated that control of the polymer-

ization time of the embolic mixtures is facilitated by adjusting the quantity of GAA. It was shown from these experiments that the polymerization time of the liquid adhesive is linearly dependent on the amount of GAA added. Furthermore, it was shown that increased concentrations of iophendylate oil in the embolic mixture also delayed the polymerization time.

Previous experiments have ascertained that both GAA and ethiodized oil delay the polymer reaction. The purpose of this study was to test two hypotheses in a controlled in vivo experiment: 1) that increased Lipiodol concentrations delay the amount of time required to embolization, and 2) that increased quantities of GAA within mixtures of Histoacryl delay the amount of time required to embolization.

Methods

Animal Model and Experimental Methods

Embolization of the left femoral and subclavian arteries was performed in 42 White New Zealand rabbits of mixed sex, weighing between 2 and 5 kg. All animal procedures were reviewed and accepted by the Institutional Animal Care and Use Committee of the State University of New York at Buffalo. With the animals under anesthesia, the right femoral artery was isolated and a femoral catheterization port was created with a 4-French sheath. Once the introducer was placed, the sheath was secured and a flush of heparinized saline (0.9% normal saline, 200 U/L heparin) was established. A bolus of heparin (50 U/kg) was administered intra-arterially to prevent clot formation during the intervention. Note importantly that the average pH value of rabbit arterial blood is reported to be 7.35.

The left femoral and subclavian arteries were exposed to allow the positioning of perivascular ultrasonic flow probes (Transonic Systems, Ithaca, NY). After probe placement, a microcatheter was navigated under fluoroscopic guidance into the origin of the contralateral femoral artery (Fig 1A), which was later found to have an inner diameter of 1.3 ± 0.49 mm. The microcatheter was placed in a free-floating position. Two different microcatheters were used for the embolization of the left femoral artery: the Tracker 18 (Target Therapeutics, San Jose, CA) and the Jetstream-18 (Medtronic, Minneapolis, MN), with distal tip diameters of 2.7- and 2.5-French, respectively. In the event of vessel spasm, a local injection of papaverine hydrochloride (0.1 cc of 30 mg/mL papaverine hydrochloride in 0.9 cc of 0.9% normal saline) during 20 min was administered through the microcatheter. If subsequent digitally subtracted angiography revealed that the spasm had not resolved, another papaverine injection was administered. No ad-
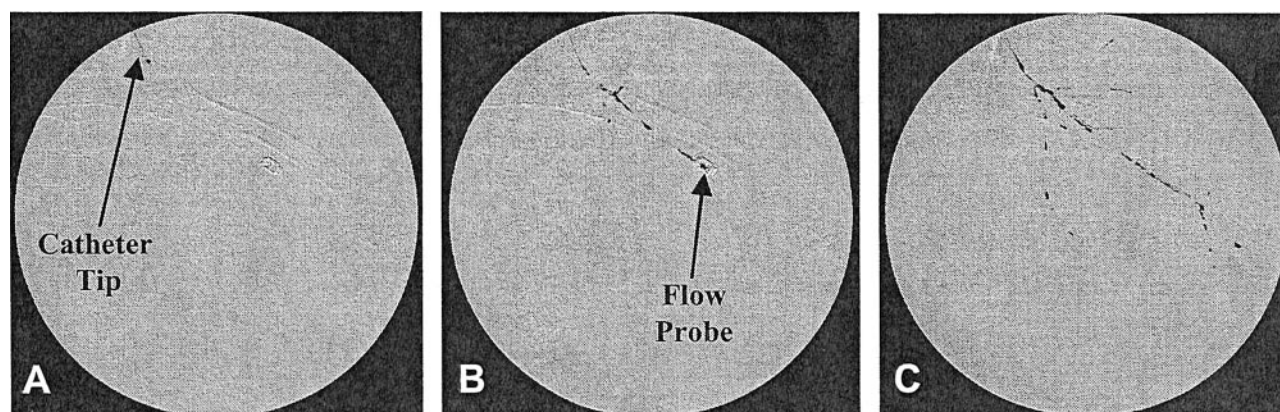
FIG 2.   Digital subtraction angiograms show different stages of the embolization procedure in a femoral artery.
  A, Injection begins as a drop of the glue mixture forms at the catheter tip.
  B, Midway through the embolization procedure, the glue mixture penetrates the ultrasonic beam of the flow probe.
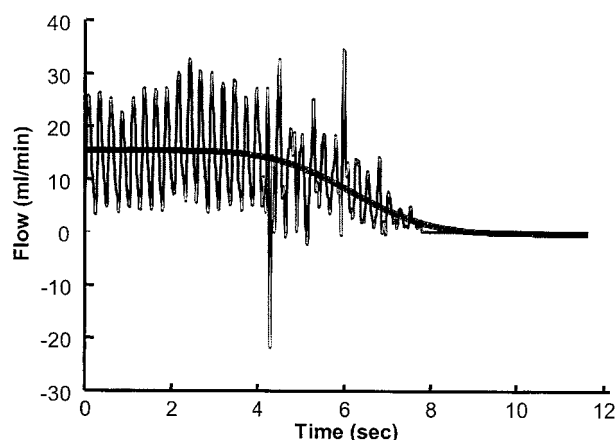 *C*, Glue mixture has completely polymerized, leading to flow cessation in the artery.

FIG 3.   Flow data acquired during embolization of the femoral artery of the rabbit after filtering. *Thick black line* depicts the reflected, optimized model fit superimposed on the filtered flow data. Model is representative of the mean flow.

verse sequelae as a result of the administration of papaverine hydrochloride were observed.

Just before embolization of the left femoral artery, the microcatheter was flushed with 3 cc of 5% dextrose solution to avoid premature polymerization of the glue inside the microcatheter. Various stages of the embolization of the femoral artery are depicted in Figure 2. Throughout the embolization procedure, the flow in the artery was recorded (Fig 3).

The preparation and embolization of the subclavian artery was performed in precisely the same manner as for the femoral artery. The subclavian arteries had an average inner diameter of 1.08 ± 0.29 mm. The catheters used for the embolization of the subclavian artery were smaller than those for the femoral artery and included the 2.0-French Tracker 10 (Target Therapeutics), 1.5-French Magic (Balt, Monmorency France), 1.8-French Jetstream-10 (Medtronic), and 1.8-French Ultralite (Medtronic). The catheter tip was placed proximally to the thyrocervical and costocervical arteries and distally from the vertebral and internal thoracic arteries in a free-floating position (Fig 1B). It is noteworthy that the right subclavian artery was not incorporated in the experiment because of the tortuosity of the artery.

After the embolization procedure was completed, the animal was killed by an IV administered overdose of sodium pentobarbital (100 mg/kg). The embolized arteries were then harvested for subsequent histologic analysis. The arteries were immediately placed in a 10% formalin solution for storage.

The NBCA used is under the trademark Histoacryl (B. Braun Melsungen AG, Germany). The ethiodized oil was Lipiodol Ultra-Fluid (Guerbet, France). Three volumetric ratios of ethiodized oil-NBCA were investigated: 50:50, 65:35, and 80:20 (percent by volume). Each mixture was tested without and then with the addition of 20 and 40 μL of GAA. The amount of GAA added was noted per milliliter of Histoacryl. The oil-NBCA ratios and the amount of GAA included were selected based on those used at our clinical affiliation. A minimum of six vessels in each of the nine data sets was required to obtain statistically significant results (28).

Data Acquisition and Analysis

During the experiment, three parameters were recorded: the vessel diameters, the pressure within the femoral and subclavian arteries before embolization, and the flow through the aforesaid arteries before, during, and immediately after embolization. The diameters of the femoral and subclavian arteries were obtained with a Toshiba Super Angiorex Model G angiography unit (Toshiba America Medical Systems, Tustin, CA), during diagnostic digital subtraction angiography runs at 3 fps. A radiopaque marker with known dimensions was used to provide an accurate scale for vessel diameter measurements.

The pressure was obtained by an established technique with which the microcatheter is connected to a pressure transducer (29). The measured pressure is related to the local mean arterial pressure. The damping of the microcatheter does not permit resolution of the pressure waveform. The variable reluctance pressure transducer (Validyne, Northridge, CA) is able to measure pressures as high as 258 mmHg, with an accuracy of 0.64 mmHg. The recorded pressure data was then averaged to yield a value for the pre-embolization mean arterial pressure.

Flow measurements were obtained with perivascular ultrasonic flow probes connected to a T-206 flow meter (Transonic Systems). Volumetric flow through the blood vessel is obtained by measuring the transit time of an ultrasonic beam. This flow measurement technique is considered the criterion standard for measuring flow in biological systems. During embolization, the flow measurements were recorded at a sampling rate of 100 Hz. The signal was preconditioned using an analog amplifier with gains of 1, 5, 10, and 20 as needed. Furthermore, a low pass filter was applied with a cutoff at the Nyquist frequency of 50 Hz, to avoid aliasing.

The flow signals acquired during embolization of the femoral and subclavian arteries contained high frequency, high amplitude noise. The noise was generated by the glue mixture traversing the ultrasonic beam emitted by the flow probe. This was unavoidable, because the acoustical properties of the po-

lymerizing embolic agent are different from those of blood. Using the maximum entropy method (Matlab; Math Works, Inc., Natick, MA), the power spectrum of the flow data was obtained. Harmonics of the fundamental frequency were identified in the power spectrum as narrow band spikes. Significant harmonics were considered to be those that had amplitudes >35 dB below that of the fundamental frequency. The last significant harmonic was considered to be the cutoff frequency. The data were thereafter low pass filtered with a 12th order Butterworth filter, using the corresponding cutoff frequency in each case. After the filtering procedure, the data were prepared for mathematical modeling.

The objective of the data analysis was to model the behavior of the mean flow during embolization of the femoral and subclavian arteries of the rabbit. To examine the stated hypotheses, it was speculated that variations of a parameter of the model fitted to the acquired flow data would reflect the changes in the time required to achieve flow arrest for each of the various glue mixtures. Therefore, the aim of this stage of the analysis was to find the most parsimonious model, wherein differences in one of the model parameters would correlate to changes in occlusion time for the different glue mixtures.

After an arduous selection process, the model chosen is an integral of a gaussian probability distribution function,

$$1) \qquad f(t) = \delta + \frac{\rho}{\sigma\sqrt{2\pi}} \int_0^t \exp\left[\frac{-(\tau-\mu)^2}{2\sigma^2}\right] d\tau$$

where δ accounts for the electronic zero flow offset, ρ is the magnification coefficient, σ is the SD, and μ is the mean. The equation of the model is related to the error function multiplied by half of the magnification coefficient,

$$2) \qquad f(t) = \delta + \frac{\rho}{2}\left[erf\left(\frac{t-\mu}{\sqrt{2}\sigma}\right) + erf\left(\frac{\mu}{\sqrt{2}\sigma}\right)\right].$$

Hence, the total number of model parameters is four.

The model parameters were then obtained using a constraint optimization program that minimized the difference between the experimental data and the model in a least squares sense (Matlab). The optimized model was applied directly to the half-range expansion of the flow data. From this representation, a physical understanding of the model parameters can be developed (Fig 3). At this juncture, that the model characterizes the behavior of the mean flow can be observed. The magnification factor, ρ, arises from the mean blood flow before embolization. Shifting the model in time was achieved by varying the mean (μ) of equation 1. The parameter that characterized the decay of blood flow to zero was the standard deviation (SD) (σ), coined the time elapsed to flow arrest (TEFA) factor.

Although the model appeared to closely follow the trend of the mean flow, a goodness-of-fit test was deemed to be of merit to quantify the degree of agreement between the model and the mean flow. To build a history of the mean flow, the half-range expanded data were low pass filtered with a 6th order Butterworth digital filter and a cutoff frequency that was an integer multiple of the lowest frequency present in the data, namely the reciprocal of the period of the data record. Filtering at such a low frequency (0.29 Hz) produced significant edge effects in the data record. However, the mean flow in the region of interest, the flow decay, was obtained. After isolating the low frequency trend of the experimental data, it was compared with the behavior of the model at the aforementioned region of interest. An excellent linear correlation was found between the model and the low pass filtered experimental data, with a coefficient of determination of 0.995 and a Pearson coefficient of 0.998. Furthermore, the slope of the linear regression (1.01) indicated that the model and the mean flow were nearly identical. The result of this analysis strongly enforces the conclusion that the mathematical model was appropriately selected to characterize the mean flow decay observed experimentally. Significance was set at $P < .05$.

Results

For the entire data set, the averaged mean arterial pressure was 44.7 ± 10 mmHg. The variation of pressure among the groups studied was insignificant ($P = .57$), as determined by a one-way analysis of variance.

Postoperatively, the diameters of the embolized vessels were measured using images acquired during digital subtraction angiography. The average inner vessel diameter was 1.2 ± 0.4 mm. The femoral artery of the rabbit was measured to be an average of 20% larger than that of the subclavian artery. A one-way analysis of variance revealed no statistically significant variation in the measured vessel diameters among the glue mixture groups ($P = .77$).
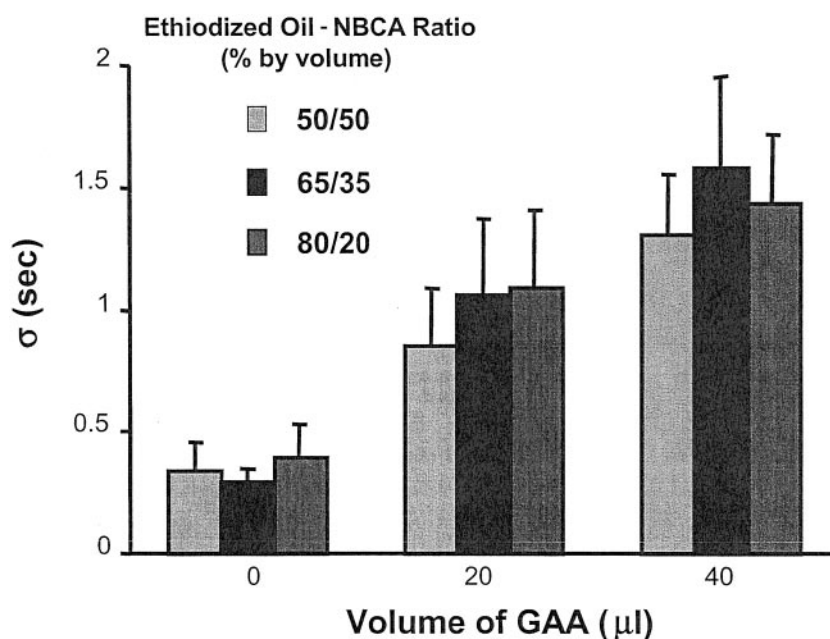
The mean pre-embolization flow was determined from the aforementioned flow records. The mean arterial blood flow measured throughout the course of the experiments was 7.2 ± 4.3 mL/min. The average blood flow in the femoral artery was nearly twice that through the subclavian artery. The variation from the mean values of the flow data was statistically insignificant among the data sets, with a P value of .77 obtained from a one-way analysis of variance test.

It has been hypothesized that by increasing the concentration of ethiodized oil in the glue mixture, polymerization is delayed (9, 15, 20, 27). The proposed mechanism for the delay of polymerization is that the ethiodized oil reduces contact of the NBCA with the blood, which inhibits the initiation of polymerization (9, 20). To determine whether the delay in polymerization time resultant of increased ethiodized oil concentration would lead to a likewise delay in the embolization of the vessel, the TEFA factor extracted from the optimized model fitted to the experimental data was compared with the oil-NBCA ratio. A statistical analysis of the data presented graphically in Figure 4 revealed that there is no significant variation ($P > .05$) of the TEFA factor with different ethiodized oil-NBCA ratios with the same amount of GAA.

The addition of minute quantities of GAA in the glue mixture has been reported to increase the polymerization time (20, 21, 27, 30). This observed phenomenon has been speculated to arise because of the neutralization of the basic environment of the blood, resulting in delayed initiation of polymerization, and the premature monomer termination with the electrophilic ions of GAA (21). To test the hypothesis that GAA increases the time to blood flow arrest during the embolization procedure, the TEFA factor was compared with the quantity of GAA added to a particular oil-NBCA mixture (Fig 4).

A statistical analysis of the data revealed that the variations of the TEFA factors among groups of the same oil-NBCA ratio but with different amounts of GAA were significant. For oil-NBCA ratios of 50:50 and 80:20 (percent by volume), a one-way analysis of

FIG 4. TEFA factors (σ) for the glue mixtures tested. Oil-NBCA ratios are provided in percent by volume, and indicated volume of GAA is per milliliter of NBCA. *Error bars* indicate standard error of the mean.

variance test produced significant *P* values of 0.016 and 0.037, respectively. For the oil-NBCA ratio of 65:35, a Kruskal-Wallis test (nonparametric analysis of variance) produced a very significant *P* value of .008. The nonparametric analysis of variance test was required because the analysis of variance test assumes that the SDs among the groups with different amounts of GAA in the glue mixture are equal. However, the data contained within the oil-NBCA group of 65:35 had extremely significant SDs, as determined by method of Bartlett. Therefore, a nonparametric analysis of variance test was used because the aforesaid assumption was violated.

It has been reported in the literature that the variation of polymerization time depends linearly on the amount of GAA added to the glue mixture (20). A similar relationship is posited to exist between the TEFA factor and the amount of GAA included in the glue mixture. To examine a possible linear trend between the aforesaid parameters, a linear regression analysis was conducted. The results are presented in Figure 5. This analysis shows that between 59% and 67% of the variation in the calculated TEFA factors exhibits a linear relationship with the quantity of GAA incorporated into the glue mixture, depending on the volumetric ratio of oil-NBCA. Although a linear model may not completely resolve the relationship of the TEFA factor to the amount of GAA, the slope of the regression lines presented in Figure 5 was found to be significantly different from zero.

Discussion

Previous research has indicated that increased concentrations of ethiodized oil in embolic mixtures containing cyanoacrylates delays the polymerization process. However, the experimental results provide evidence that the time required for the glue mixture
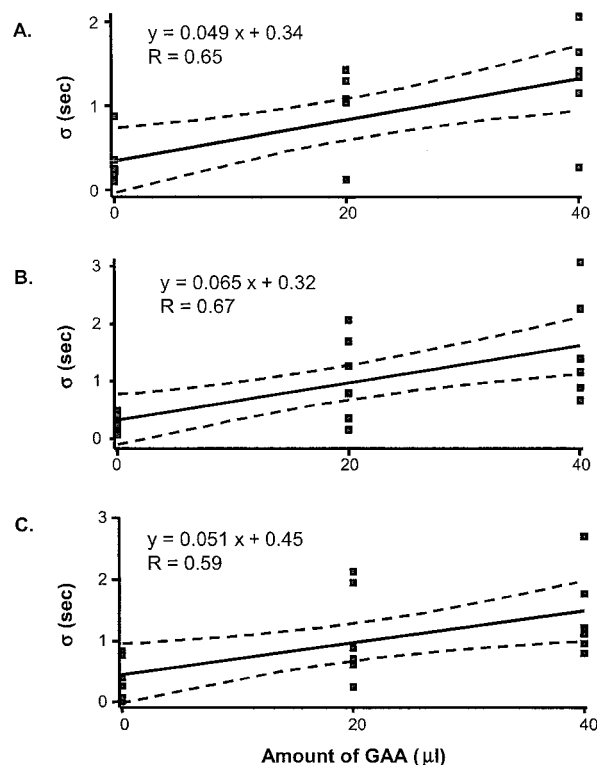

FIG 5. Linear regression analysis performed on the TEFA factor (σ) plotted versus the quantity of GAA added to the glue mixture (per milliliter of NBCA). Plots are separated by the percent by volume of ethiodized oil compared with that of cyanoacrylate. Regression line (*solid line*) is shown in each plot, with corresponding equation and Pearson correlation coefficient provided. The 95% confidence interval lies between the *dotted lines*.
  A, 50:50.
  B, 65:35.
  C, 80:20.

to arrest blood flow via polymerization is independent of the ethiodized oil concentration, with the caveat that the oil-NBCA ratio lies within the range exam-

ined in this study. This result seems to contradict the accumulated knowledge from previous polymerization time studies of embolic mixtures containing cyanoacrylates (9, 15, 20, 27, 31). Brothers et al (20) reported that the polymerization time varies linearly with the concentration of iophendylate oil. However, a statistical analysis of the different ratios of iophendylate oil-NBCA was not provided in the report. Furthermore, Brothers et al show that increasing the oil concentration from 50% to 66.7% by volume of the glue mixture does not increase in the polymerization time. A further increase of iophendylate concentration to 75% yielded an increase in polymerization time from approximately 2.6 ± 0.7 s to 4.1 ± 0.7 s.

The observed independence of time to flow arrest on the oil-NBCA ratio in this study may be explained by the physical changes that occur as the concentration of ethiodized oil is increased in the glue mixture. Lipiodol Ultra-Fluid has a viscosity that is similar to that of pure vegetable oil (as reported by the manufacturer). Using a rheometer (Brookfeld, Middleboro, MA), the viscosity of Lipiodol Ultra-Fluid was measured at 15°C, 25°C, and 37°C, and the viscosities were an average of 42cP, 26cP, and 17 cP, respectively. The viscosity of NBCA has been reported in the literature to be 3.2 cP (32). Therefore, the viscosity of the glue mixture increases proportionately with increases in the concentration of ethiodized oil.

It is postulated that the change in the physical properties of the different oil-NBCA mixtures alters the time required for the embolic agent to arrest blood flow. Although increased concentrations of ethiodized oil in the glue mixture may delay the polymerization of the glue mixture by buffering the contact of blood anions with the NBCA, no statistically significant difference was observed in the TEFA factor among groups with different ratios of oil and NBCA. This result suggests that as the viscosity of the glue mixture increases, the required degree of polymerization of the NBCA to lead to blood flow arrest in the subclavian and femoral arteries of the rabbit is reduced.

As the glue mixture polymerizes, the process of embolization is essentially the result of two mechanisms, namely a time-dependent increase of viscosity of the embolic agent and adhesion of the polymer to the vessel wall. Eventually, the cast cures completely and the viscosity of the then solid embolic agent tends toward infinity. By using a glue mixture with a high concentration of ethiodized oil (ie, 80:20), the initial viscosity is increased. Thus, a smaller amount of polymer chain density and forces exerted on the flow by adhesion will provide the critical resistance to blood flow, which results in blood flow cessation. In contradistinction, a glue mixture with a relatively small ethiodized oil concentration (ie, 50:50), has a lower initial viscosity than does the previous example. However, with less ethiodized oil to buffer the contact of NBCA with blood anions, the polymerization of the mixture may be assumed to proceed at a more rapid rate. Thus, there is interplay of the flow physics and the chemical reaction of the glue mixture, which in-

fluences the time required to stop the flow of blood within the artery. It is speculated that the insignificant variation of the TEFA factor with ethiodized oil concentration in the glue mixture is a manifestation of the interaction between the chemical and physical mechanisms by which the embolic agent provides sufficient flow resistance to achieve flow arrest.

The hypothesis that the TEFA factor depends on the amount of GAA added to the glue mixture has been confirmed by the results presented herein. Furthermore, the postulate that the dependence is linear has been supported by a linear regression analysis. The mechanism by which the GAA increases the TEFA factor may be speculated to arise by inhibiting the initiation of the polymerization process by neutralizing the availability of blood anions (21). Furthermore, the presence of GAA in the glue mixture may lead to monomer termination. In this scenario, fewer monomers would be available to form a polymer chain leading to reduced adhesion of the polymer to the vessel wall and hence an increase in the time to flow arrest. Because GAA is added to the embolic agent in minute quantities, there is no appreciable change in the viscosity of the oil-NBCA mixture. Hence, the delay of polymerization due to the addition of GAA translates to a proportionate increase in the time required to achieve occlusion.

Perhaps the most significant limitation of this investigation is the use of the femoral and subclavian arteries of the rabbit to study the polymerization process of glue mixtures used in the embolization of brain AVMs. These arteries were selected for a myriad of reasons, not the least of which was a result of practical considerations regarding the ease of surgical accessibility. Furthermore, these arteries provided similar diameters to those typically found in the feeding arteries of the AVM nidus and even in some of the larger intranidal vessels. However, the femoral and subclavian arteries are straight vascular segments that do not offer the complex geometry of vessels found in plexiform AVMs. Thus, the blood flow through a cerebral AVM is dramatically different from that observed in the femoral and subclavian arteries of the rabbit.

Currently, animal models, such as swine and sheep, offer a vascular anatomic feature that closely resembles the morphology of a human plexiform AVM. This vascular formation, which is termed the rete mirabile, is often used to study endovascular embolization as applied to human AVMs. The methodology of measuring peri-embolization flow in the retia mirabile is a natural progression of the work presented herein.

The objective of this work was to investigate the effect that various concentrations of ethiodized oil along with the addition of different amounts of GAA had on the embolization time of the glue mixture. Although the embolization time of the glue mixture in a human AVM may be markedly different from those found in this study, the observed trends are thought to be applicable to embolotherapy of cerebral AVMs.

Conclusion

Methods of in vivo experimentation and data analysis are presented, with the objective to elucidate information regarding the embolization process of various glue mixtures, which are used clinically in the endovascular embolization of AVMs. The transient decay of flow to zero throughout the embolization procedure was modeled, and one of the model parameters, σ, was termed the TEFA factor. The TEFA factor has been posited to signify the time elapsed between glue mixture injection and subsequent flow arrest. The results presented herein show that the TEFA factor is independent of the variation of the ethiodized oil in the glue mixture and that the addition of GAA significantly increases, with a linear relationship, the TEFA factor.

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