Polyvinyl Alcohol Particle Size and Suspension Characteristics

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PURPOSE: To evaluate the size and shape of commercially available polyvinyl alcohol (PVA) particles and to determine whether they change in size when suspended in nonionic contrast and in a solution of nonionic contrast and absolute alcohol. **METHODS:** The two-dimensional area and the long and short axis of PVA particles from several different vendors were measured using a light microscope attached to a video system and an image-processing software program. Particles were measured as packaged (dry or suspended in saline), suspended in ioversol, and suspended in ioversol containing 30% alcohol. **RESULTS:** All brands of dry particles had similar microscopic appearances. The saline-suspended particles had fewer and finer perforations. After suspension in contrast, all sizes and brands of dry particles significantly increased in size. The particles packaged in saline did not expand. The addition of alcohol to the contrast did not consistently change particle size. Particle aggregation was similar in both contrast suspensions for all groups of particles. Particles less than 50 μm in size were rarely observed in any PVA preparation after suspension. **CONCLUSIONS:** The three dry PVA preparations seen to be similar. All increase significantly in size when suspended in nonionic contrast or contrast-alcohol solutions. The saline-packaged PVA particles were different from the dry variety and did not enlarge in contrast or contrast-alcohol solutions. Alcohol did not change the size or suspension characteristics of PVA particles. Particles less than 50 μm in size were rarely identified.

Index term: Interventional materials, particles and microspheres

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Catheter occlusion during an embolization procedure is frustrating and will unnecessarily prolong a procedure if a new catheter must be placed, which increases the risk and cost. Catheter occlusion during embolization procedures occurs more frequently with larger particles. Polyvinyl alcohol (PVA) has been used as an embolic material for more than 20 years, and several articles have described techniques to suspend the particles better and avoid aggregation, which is often blamed for catheter occlusion. Some practitioners have advocated a dual syringe technique (1), others have described suspending the particles in albumen and dextran (2), and yet other groups have described combining PVA with absorbable gelatin sponge (Gelfoam) (3) or Avitene and 30% absolute alcohol (4). This variety of approaches attests to some difficulty in using PVA suspensions.

In our experience, the addition of small amounts of absolute alcohol to the suspension of PVA in nonionic contrast seemed to reduce the incidence of catheter occlusion. We undertook this experiment to test the hypothesis that the addition of alcohol made the PVA particles in contrast media suspension smaller or altered their aggregation, thus accounting for the apparent reduction in catheter occlusion. As part of this investigation, it was necessary to understand the size, morphology, and behavior of PVA particles in suspension. An evaluation of the similarities and differences between com-

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Results of PVA particle measurements (in μm)

PVA (Biodyne)	200–300 Dry	200–300 Contrast	200–300 Alcohol	300–500 Dry	300–500 Contrast	300–500 Alcohol	500–700 Dry	500–700 Contrast	500–700 Alcohol	700–1000 Dry	700–1000 Contrast	700–1000 Alcohol
Sample size	56	45	76	187	169	105	128	113	125	157	97	54
Mean minimum axis	257	358*	367*	429	489*	511*	613	802*	785*	825	1138	1108*
SD	49	64	71	91	119	96	88	148	157	148	141	150
Change vs dry	...	39%	43%	...	14%	19%	...	31%	28%	...	38%	34%
Mean maximum axis	487	558*	586*	715	726	805*	897	1105*	1082*	1157	1518*	1495*
Mean area, mm^2	0.099	0.167*	0.162*	0.246	0.284*	0.319*	0.430	0.691*	0.667*	0.756	1.349*	1.305*

Ivalon (iValon)	200–300 Dry	200–300 Contrast	200–300 Alcohol	300–500 Dry	300–500 Contrast	300–500 Alcohol	500–700 Dry	500–700 Contrast	500–700 Alcohol	700–1000 Dry	700–1000 Contrast	700–1000 Alcohol
Sample size	91	35	42	93	53	47	91	55	42	94	34	35
Mean minimum axis	269	320*	354*	434	492*	579*	598	788*	900*	858	1203*	1198*
SD	49	53	68	79	94	90	67	109	158	89	145	125
Change minimum axis	...	19%	32%	...	13%	33%	...	32%	51%	...	40%	40%
Mean maximum axis	443	508*	534*	655	786*	802*	854	1083*	1112*	1209	1561*	1510*
Area, mm^2	0.095	0.179*	0.141*	0.231	0.307*	0.358*	0.403	0.674*	0.779*	0.814	1.474*	1.420*

Contour (Interventional Therapeutics)	150–250 Dry	150–250 Contrast	150–250 Alcohol	500–710 Dry	500–710 Contrast	500–710 Alcohol	710–1000 Dry	710–1000 Contrast	710–1000 Alcohol
Sample size	91	76	82	92	43	60	81	48	35
Mean minimum axis	206	253*	240*	583	725*	727*	858	1114*	1095*
SD	33	56	44	78	104	111	84	159	150
Change minimum axis	...	23%	17%	24%	24%	...	30%	28%	...
Mean maximum axis	313	376*	375*	851	1106*	1044*	1251	1512*	1495*
Area, mm^2	0.051	0.075*	0.071*	0.394	0.619*	0.589*	0.839	1.367*	1.301*

Ivalon (Nycomed Ingenor)	150–300 Saline	150–300 Contrast	150–300 Alcohol	300–600 Saline	300–600 Contrast	300–600 Alcohol	600–1000 Saline	600–1000 Contrast	600–1000 Alcohol
Sample size	90	87	65	72	43	39	40	45	56
Mean minimum axis	199	214	216	351	319	321	437	448	462
SD	47	41	51	101	94	82	81	91	77
Change minimum axis	...	8%	9%	...	−9%	−9%	...	3%	6%
Mean maximum axis	297	340	318	571	516	525	607	663	631
Area, mm^2	0.047	0.056	0.051	0.158	0.132	0.134	0.211	0.235	0.192

* Statistically significant ($P < .05$) comparing contrast medium or contrast and alcohol groups with the dry group.
** Statistically significant ($P < .05$) comparing the contrast and alcohol group with both the dry and contrast-only groups.

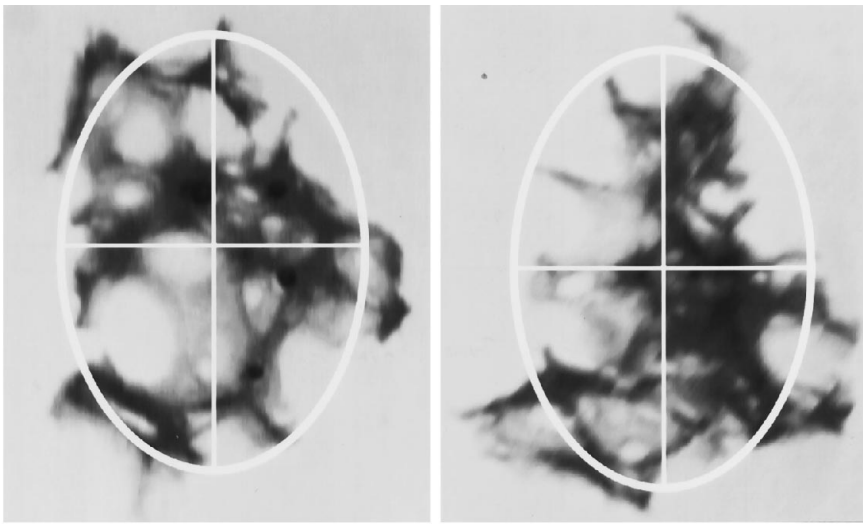

Fig 1. Examples of best-fitting ellipses and major and minor axes superimposed on videotaped 500-μm PVA particles suspended in contrast.

mercially available PVA preparations became a secondary aim of this project.

Methods

PVA particles from four vendors were examined (Table).These included 200- (200- to 300-), 300- (300- to 500-), 500- (500- to 700-), and 700- (700- to 1000-) μm PVA particles from Biodyne (El Cajon, Calif); 200- to 300-, 300- to 500-, 500- to 700-, and 700- to 1000-μm Ivalon from iValon (San Diego, Calif); 150- to 250-, 500- to 710-, and 710- to 1000-μm Contour from Interventional Therapeutics Corporation (Fremont, Calif); and 150- to 300-, 300- to 600-, and 600- to 1000-μm Ivalon particles from Nycomed Ingenor (Paris, France). The PVA from the first three manufacturers was packaged as 100-mg dry particles in sterile vials. The Nycomed Ingenor product came as 100 mg of PVA in 4 mL of a 0.9% sodium chloride solution in a 5-mL vial. Nycomed Ingenor's dry PVA preparation, Drivalon, has been discontinued. All vials were for clinical use and remained sealed until the time of study. Previously opened stock or expired samples were not used. The Biodyne and Interventional Therapeutics samples were from stock at our institution. The iValon particles were donated by their manufacturer. The Nycomed Ingenor samples were donated by their distributor, Yokan Medical Systems (Toronto, Ontario, Canada).

An inverted microscope (Nikon Diaphot, Nikon, Garden City, NJ) with a 2× lens (Nikon Lens 2XFL) was used to image the particles. A charge-coupled device camera (CCD-72, Dage-MTI, Michigan City, Ind) connected to an image intensifier (Genesis II, Dage-MTI) formed and amplified the video signal, which was recorded on a videorecorder (Panasonic S-VHS videorecorder 1960, Panasonic, Secaucus, NJ).

The videotaped particles were analyzed using an image-processing software program (Image 1.49, Wayne Rasband, National Institutes of Health, Bethesda, Md) to measure the maximum and minimum axis of the best-fitting ellipse of each particle (ellipse routines and notes by Bob Rodieck, University of Washington). The program was calibrated with a microscopic 1-mm ruler with 10-μm gradations at the start of each series of measurements. Each discrete particle was assigned a color using a threshold command, which assigns a color to any object on the screen above a preset minimum optical density. The threshold was set to characterize the area of each particle optimally. The program counts the number of pixels in each outlined particle to obtain the area. The best-fitting ellipse that the program generates has the same area as the particle measured. The major and minor axes define the shape of the ellipse (Figs 1 and 2).

Particles were measured as packaged, suspended in ioversol (Optiray 320, Mallinckrodt Medical, St Louis, Mo), and suspended in 30% alcohol in ioversol. The PVA-contrast suspension was prepared as recommended by the manufacturer: Ten milliliters of contrast media were injected into a sealed bottle of particles or were mixed in a bowl with the saline-suspended particles. For 10 minutes, the bottle or bowl was occasionally gently swirled, and then a few drops were placed on a slide with a large-bore pipette. For the contrast and alcohol suspension, 3 mL of absolute alcohol was added to 7 mL of contrast media in the PVA bottle or bowl, and the same procedure was followed. Under the microscope, particles were separated using a 25-gauge needle. This prevented the accidental measurement of aggregated particles as a single particle.

For statistical analysis, the measured parameters of each PVA group were compared using a microcomputer software program (Instat 2.0 GraphPad Software, San Diego, Calif). The histograms of the data were not consistently gaussian, so the Kruskall-Wallis nonparametric analysis of variance test was used, because it makes no assumption about the scatter of data (ie, gaussian distribution). Subsequently, Dunn's multiple-comparison test was used to identify statistically significant differences between each PVA subgroup. Data are represented as mean values ± SD. Statistical significance was accepted at $P <$ .05.

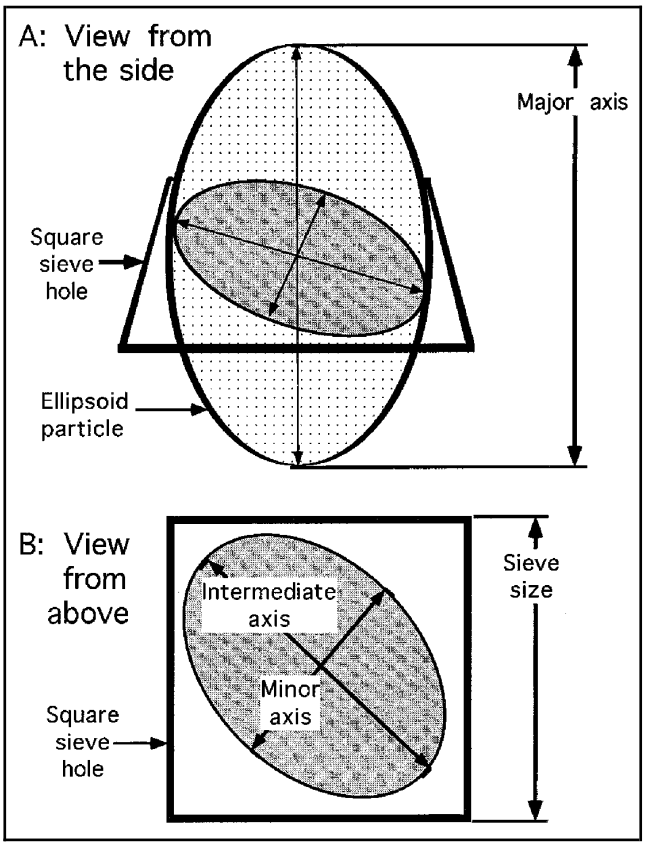

Fig 2. Diagram of a hypothetical particle passing through a square sieve hole. The major axis lines up perpendicular to the plane of the sieve in the lateral view (*A*). The minor and intermediate axis are shown from above in *B*. The major and minor axes do not determine the particle's ability to pass through the sieve as much as the intermediate axis. (Adapted from a drawing courtesy of Joseph A. Horton, MD.)

Results

The pattern of distribution of minimum and maximum axes was similar for all brands of PVA. Representative histograms of the Biodyne PVA particles are shown in Figure 3. The mean data for all particle groups are shown in the Table. The mean minimum axes of the dry particles were similar to advertised minimum sizes. For example, the mean minimum axis of dry 200-μm Biodyne particles was 260 μm (Table). The range of minimum axes for each particle group for Biodyne can be observed in Figure 3 (white bars). Few dry particles had dimensions that were smaller than the advertised minimum size. However, many dry particles had minimum axes larger than the advertised maximum dimension (Fig 3).

Once suspended in contrast, the dry particles enlarged. The mean axes of each PVA group suspended in contrast increased compared with the mean axes of the dry particles. This increase in size was statistically significant for all PVA groups (Table). Figure 4 demonstrates the mean minimum axis of each group of particles with SD bars, graphically demonstrating the increase in dry particle size after suspension in contrast medium. The dry size and degree of enlargement in solution among the three dry PVA preparations were comparable.

The addition of alcohol did not result in a statistically significant difference in size compared with contrast suspension alone in 36 of 42 sample groups (Table). Only in the mean minimum axes and areas of 300- to 500- and 500- to 700-μm Ivalon and in the mean maximum axis and area of Biodyne 500–700 PVA were statistically significant increases observed. No significant decrease in size of the particles was observed in any of the samples.

The saline-suspended Nycomed particles did not significantly change when suspended in contrast or contrast-ethanol.

The microscopic appearance of the dry PVA was similar (Fig 5). Rarely, particles smaller than 50 μm were observed in all preparations after suspension (Fig 5C and D). None of these small particles were observed before suspension in contrast or contrast-alcohol. These particles were not quantified because of their rare occurrence. In addition, they were best seen under the microscope and often were not visible on the videotape. Similarly, particles smaller than 50-μm were also seen in the Nycomed Ingenor particles. These saline-suspended particles contained fewer large perforations than the other particles. When probed with a needle for separation, they were more firm than the suspended dry particles. All particle groups tended to aggregate in both test solutions, and differences were not observed in this behavior between particles of the different manufacturers.

Discussion

The use of PVA particles for transcatheter embolization procedures has become widely accepted since its introduction nearly 20 years ago. The biocompatibility of PVA is well documented, as is its efficacy as a relatively permanent embolic agent (5–11). The hand preparation of these particles was time consuming, and consequently, commercial preparations of sterile, prepackaged PVA were introduced (1).

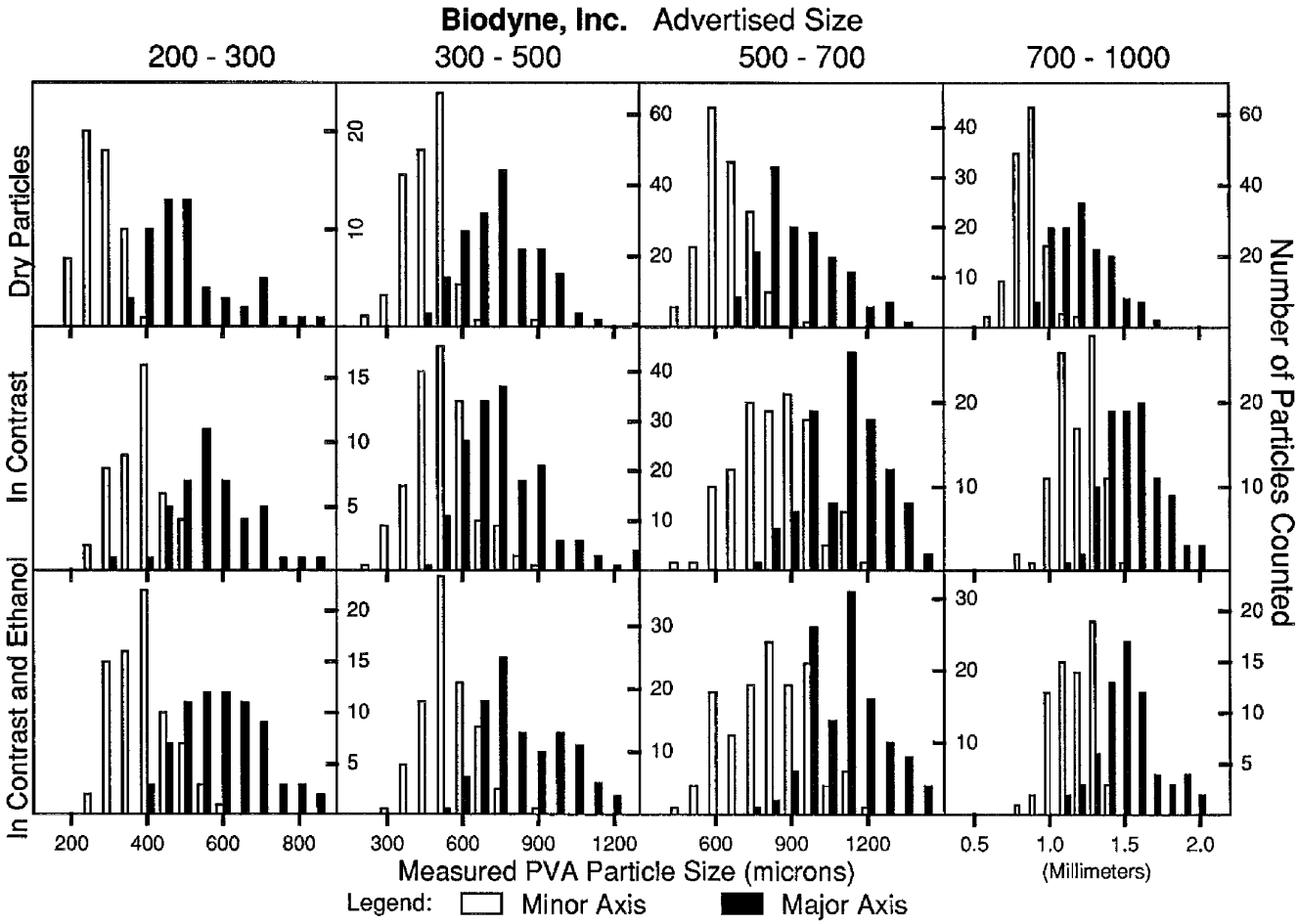

Fig 3. Histograms of major and minor axes for all Biodyne PVA particles in each preparation. *Vertical columns* from *left* to *right* are 200-, 300-, 500-, and 700-μm particles, and *horizontal rows* from *top* to *bottom* are dry, suspended in contrast, and suspended in contrast and 30% alcohol (ethanol). In each histogram, there is a wide range of particle dimensions. In each column, the particle dimensions shift rightward as they enlarge in suspension. Histograms of the PVA from other vendors demonstrated a similar range of distributions.

Before the commercially available PVA, particles were prepared by rasping or blending an Ivalon block, or by punching out plugs (2, 5, 12). Sequential calibrated sieves were subsequently used to separate the PVA shavings into uniform sizes. In this method, particles are passed through sieves of progressively finer grains. The advertised size reflects the pair of sieves through which the PVA particles passed and were stopped, respectively. For example, a 300- to 500-μm particle passed through a 500-μm sieve and was stopped by a 300-μm sieve. The sieve holes are square, and the PVA particles pass through them, primarily as a function of their intermediate axes (J.A. Horton, Medical University of South Carolina, Charleston, personal communication, 1995) (Fig 2). The major axis is perpendicular to the plane of the sieve and does not affect the ability of the particle to pass through. The minor and intermediate axes are in the plane of the sieve hole. Although the manufacturers of these PVA particles consider many of the details regarding their preparation to be proprietary information, two vendors have indicated their use of the graduated sieving method.

Despite the use of these sieves, however, many small, less than 2-μm particles were found (12). Some authors have suggested that these small particles were responsible for facial nerve palsies reported after external carotid artery embolizations (13, 14). The danger of these very small particles was underscored by a report of two deaths, which were attributed to the presence of many small (less than 20-μm) particles in a commercial PVA preparation (15). The manufacturer of the particles in this report quickly modified its technique to eliminate

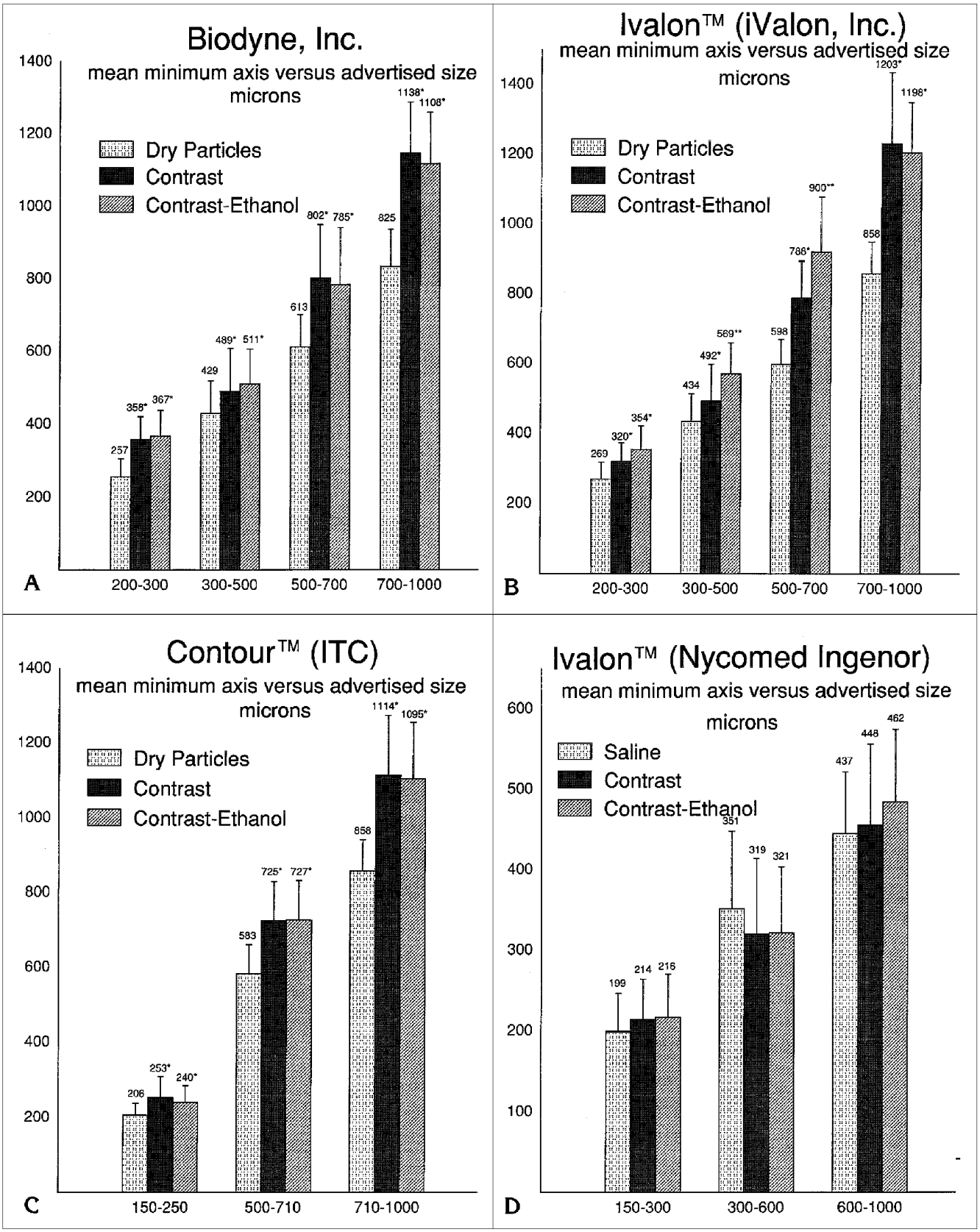

Fig 4. Mean minimum axis with SD *bars* for each particle size and preparation. *Numbers* above the SD bars indicate the actual mean minimum axis value.

* Statistically significant ($P < .05$) comparing contrast medium or contrast-alcohol groups to the dry group.

** Statistically significant ($P < .05$) comparing the contrast-alcohol group with both the dry and contrast-only groups.

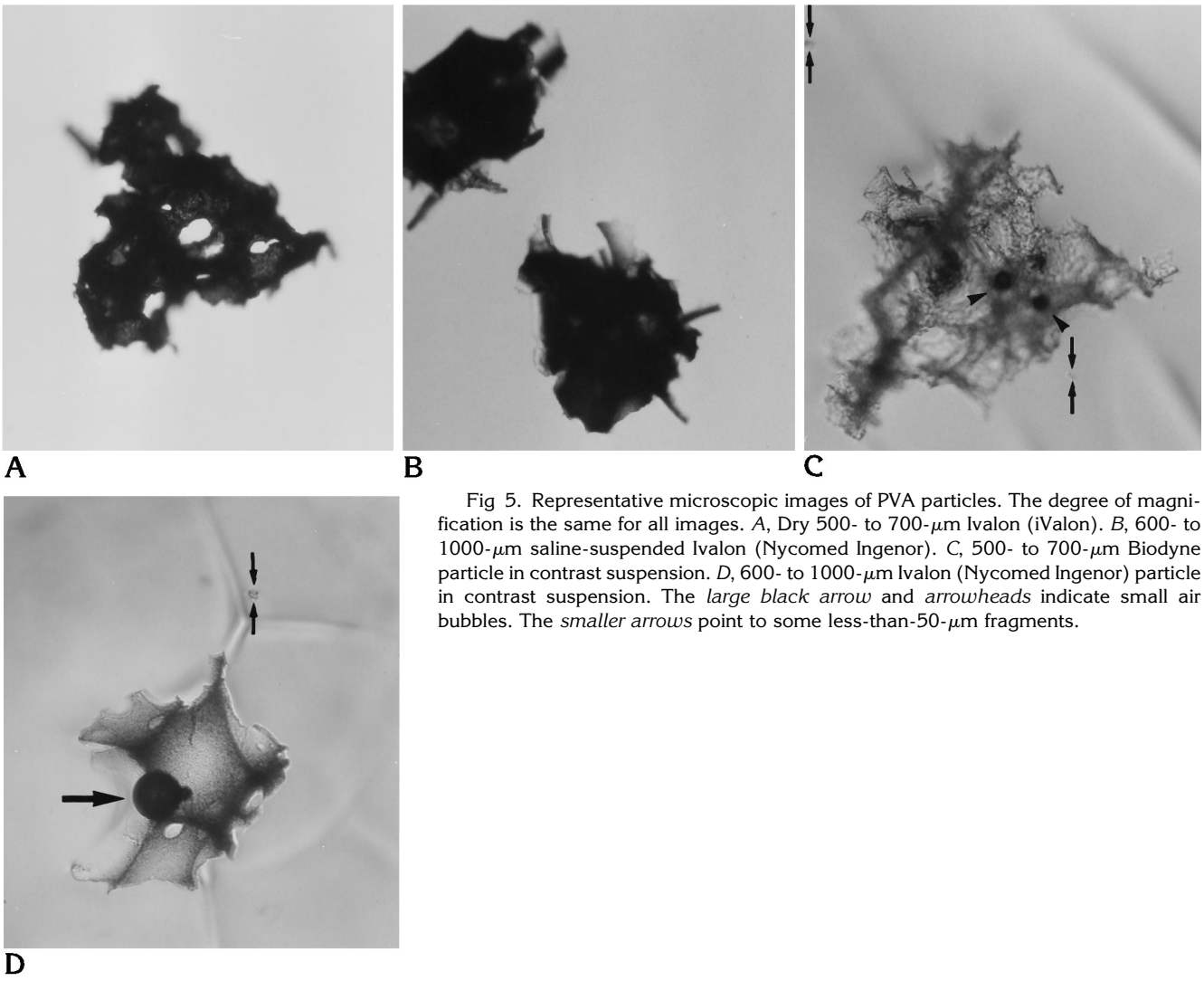

Fig 5. Representative microscopic images of PVA particles. The degree of magnification is the same for all images. *A*, Dry 500- to 700-μm Ivalon (iValon). *B*, 600- to 1000-μm saline-suspended Ivalon (Nycomed Ingenor). *C*, 500- to 700-μm Biodyne particle in contrast suspension. *D*, 600- to 1000-μm Ivalon (Nycomed Ingenor) particle in contrast suspension. The *large black arrow* and *arrowheads* indicate small air bubbles. The *smaller arrows* point to some less-than-50-μm fragments.

these small fragments (15). Although commercial preparations have gained widespread acceptance, there has not been a report, to our knowledge, describing particle uniformity and size in these preparations since the report of the two deaths in 1989.

Although very small particles were not seen in any of the dry PVA samples in this report, a few 50-μm or smaller particles were seen after suspension. This finding is interesting in light of a previous investigation by Jack et al (12), who compared homemade blended PVA with a commercially available variety. They found numerous small particles in their blender sample. No small particles were identified in the commercial preparation, but it is not clear whether they were suspended in solution. These particles may have been either adherent to or inside of the dry particles or fractured off fragments of PVA from preparation of the solution. This probably is the source of the small particles in the suspensions observed in this report. To our knowledge, there has not been a report of complications attributable to small particles since 1989, suggesting that these particles in the current preparations are not clinically significant.

We used a computer software program to make the measurement of the particles uniform and reproducible. The method used in the program is statistically validated for the characterization of two-dimensional objects (16). The area of the calculated ellipse is the same as the measured particle with a high degree of accuracy. Calibration of the imaging program using a microscopic ruler maintains accuracy. A flaw in using this method to size PVA particles is that

it measures a three-dimensional, globular object in only two dimensions. However, these particles are generally elliptical and are assumed to be lying flat on a surface when they are measured. The actual minor axis will usually be the unmeasured vertical height of the particle, whereas the actual intermediate axis will be approximated by the measured minor axis. The minimum measured axis will therefore be a conservative estimation of the intermediate axis; it will range in value between the actual minor and intermediate axes. The ability of a particle to pass through a given sieve dimension primarily depends on its intermediate axis, so the mean minimum axis was used for data analysis and presentation in Figure 4. Moreover, as long as the technique used to measure the particles is reproducible, measured changes of particle sizes should be reliable.

The two situations in which this method will not accurately estimate the dimensions are a dumbbell- and a C-shaped particle. In these instances, the measured area will be accurate, but the major and minor axes will be misrepresented. Neither of these types of particles was observed. Most particles were globular in shape (Fig 5).

Knowledge of particle uniformity and size is important for several reasons. A specific combination of catheter diameter and particle size is selected for each embolization procedure. The catheter must be flexible and small enough to allow selective catheterization of the vessel supplying the lesion and yet be large enough to deliver embolic agents. The particles must fit through the catheter without causing catheter occlusion yet not be so small that they pass through the circulation of the lesion. The selection of the optimal combination of catheter diameter and particle size therefore requires an accurate knowledge of particle dimensions and uniformity. Furthermore, larger particles are more likely to occlude the catheter. Accurate knowledge regarding the size of particles may prevent the selection of a particle size that is too large for the catheter. The data from this study indicate that dry PVA particles swell significantly when suspended in contrast or contrast and ethanol solutions. This phenomenon may contribute to catheter occlusion and should be considered when selecting the appropriate catheter and particle size. Other factors, however, likely mitigate the increase in particle size. For example, in clinical use most suspended 700-μm particles pass through a microcatheter. Because we now know that their mean minimum axes are more than 1 mm, this is likely caused by the compressibility of the suspended PVA and/or the expansion of the microcatheter. These data help explain why catheter occlusion occurs with dry particles that are advertised as smaller than the microcatheter lumen.

Why do the particles enlarge? PVA is a polyvinylic foam that behaves like a sponge in that its wet volume is greater than its dry volume. In some preparations it can be compressed to less than one tenth of its wet volume. The saline-suspended PVA is filtered wet, which most likely accounts for its lack of enlargement. The dry PVA preparations may be sieved in a compressed, dry form and subsequently enlarge in solution. Alternatively, they may be forced through the sieve while wet and then dried for packaging.

How do these data influence the choice of a PVA particle size for a particular vascular bed? If the behavior of the particles in a sieve can be extrapolated to a vessel, then the intermediate axis could also determine the diameter at which it becomes plugged. The unknown amount of compression of the particle in vivo, however, limits the ability to predict this diameter.

In our experience, the addition of a small amount of ethanol to the PVA suspension seems to reduce the frequency of catheter occlusion. Alcohol may have a role in some embolization procedures (4, 17) (Dion J, Viñuela F, Lylyk P, Lufkin R, Bentson J, ''Ivalon-33% Ethanol-Avitene Embolic Mixture: Clinical Experience with Neuroradiological Endovascular Therapy in 40 Arteriovenous Malformations,'' *AJNR Am J Neuroradiol* 1988;9:1029, abstract). We undertook this experiment to investigate the possibility that ethanol shrinks PVA particles in contrast medium suspensions, thus reducing the chance of catheter occlusion. Alcohol is an anhydrous solvent and might be expected to dehydrate and shrink a sponge. The data indicate that this hypothesis is not valid. If alcohol does reduce catheter occlusion, it may be related to effects on fluid viscosity or particle behavior in solution, such as particle compressibility and flexibility.

To our knowledge, little has been written on the chemical or physical behavior of PVA in contrast media suspensions. With a better understanding of these issues, improvements in

the transcatheter delivery of PVA may be identified. More work in this area is planned.

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