Evaluation of hydrophilic polymer embolization from endovascular sheath devices in an in vitro perfusion system

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ABSTRACT

Objective: Case reports, tissue pathology, and autopsies have suggested that the hydrophilic polymer coating designed to improve endovascular deliverability and minimize vessel trauma can embolize and be associated with adverse outcomes such as ischemia, infarction, and death. This study sought to determine whether hydrophilic polymers shed off commercially available sheaths in a controlled in vitro environment, with the hypothesis that significant differences between coated and uncoated (control) sheaths would be found.

Methods: Six sheaths from each manufacturer, including Zenith Alpha abdominal endovascular stent grafts (Cook Medical), DrySeal sheaths (W.L. Gore & Associates), and Sentrant Introducer sheaths (Medtronic), were tested in an in vitro environment. Noncoated Check-Flo performer introducer sheaths (Cook Medical) were used as controls. Each test circuit ran for 150 minutes at an output of 3 L/min, the circuit was then drained and the fluid collected. Quantitative analysis included weighing the dried filter paper and using particle size light scattering to quantify the particle size and count. Attenuated total reflectance spectroscopy was also used.

Results: Each of the three coated sheaths had significantly greater shedding compared with the control sheaths. The Cook Zenith alpha sheath had significantly more residue weight (2.87 ± 0.52 mg/L) than the Gore DrySeal (1.07 ± 0.06 mg/L) and Medtronic Sentrant introducer (0.98 ± 0.14 mg/L) sheaths. The average particle size was not significantly different between the coated and uncoated (control) sheaths. Attenuated total reflectance spectroscopy identified sheath particulate in the Cook Zenith Alpha and Medtronic Sentrant samples.

Conclusions: Polymer embolization was present and significantly greater in all three commercially available hydrophilic sheaths compared with the control group. Further investigation is needed into the clinical significance of these findings. (JVS—Vascular Science 2023;4:100127.)

Clinical Relevance: Hydrophilic polymer coatings have significantly enhanced patient outcomes after endovascular procedures. However, isolated case reports have raised concerns about the potential embolization of such coatings, leading to end-organ ischemia and damage. Our results confirm the presence of this phenomenon. This knowledge will enable patients, physicians, and manufactures to make informed decisions and take appropriate precautions. Furthermore, it is imperative to conduct further research to thoroughly characterize the embolization profile of different sheaths. Such investigations would contribute to our understanding of the problem and provide valuable information for manufactures to guide the development of safer and more reliable devices.

Keywords: Aneurysm; Clinical engineering; Endovascular aneurysm repair; Heparinized hydrophilic polymer; Postoperative complications

Since the development of hydrophilic polymer coatings, improved handling of endovascular devices and decreased trauma to vessel walls has reduced the associated morbidity and mortality with catheterization and angioplasty procedures. With the increasing trend toward minimally invasive procedures, the popularity and need for hydrophilic polymer coatings has also increased.[1] Despite its success, polymer coated materials have been found in surgical and autopsy specimens, indicating concerning embolization from their device surfaces.[2-6] An increasing body of case reports has described hydrophilic polymer embolization (HPE) events leading to various clinical sequelae, including ischemia, infarction, and death.[6-10] In 2009, one of the

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first recorded deaths clearly attributed to widespread embolization of hydrophilic polymer material was documented by Mehta et al.[7] Their report exposed hydrophilic polymers as having the potential, not only to induce local inflammatory reactions, but also to cause distal and fatal embolic damage.

To date, iatrogenic sequelae have only been described in retrospective reviews and reports following vascular interventions using coated medical devices. Three previous studies have used in vitro circuits to demonstrate stripping of the hydrophilic coating. All showed microscopic evidence of HPE from infusion microcatheters, drug-eluting stents, and a self-expanding stent and delivery system.[11-13] In the present study, we created a structured in vitro perfusion system to identify and quantify the amount of HPE from three commercially available endovascular sheaths. We hypothesized a significant difference would be found in polymer shedding between the coated sheaths and a control (uncoated) sheath. The purpose of our research is to enhance clinician awareness of the possible complications of HPE in endovascular surgery and provide feedback to manufacturers to, ideally, influence the developments and technical advances in hydrophilic coated products.

ARTICLE HIGHLIGHTS

- **Type of Research:** An in vitro study
- **Key Findings:** All hydrophilic sheaths shed polymer particles that can produce embolization. The Zenith Alpha sheath (Cook Medical) produced significantly more residue after sample filtration (2.87 ± 0.52 mg/L) than the Sentrant introducer sheath (0.98 ± 0.14 mg/L; Medtronic) and DrySeal sheath (1.07 ± 0.06 mg/L; W.L. Gore & Associates). No significant differences in average particle size were present.
- **Take Home Message:** Polymer embolization was present and significantly greater in all three commercially available sheaths vs the control.

METHODS

Flow loop design and construction. To create a flow loop of "circulation," a large animal pulsatile blood pump (model 1423; Harvard Apparatus) was used as the "heart" in the flow loop construction. The pump was used to provide flow within the loop, ensuring that the sheaths were continuously and evenly exposed to fluid within the loop. It is understood that activation and sloughing of the polymer coating does not rely on the fluid dynamics seen in systole and diastole. Instead, direct contact with the fluid alone will cause breakdown of the coating.[14]

The pump was set to a stroke rate of 80 beats/min and a voltage of 60 Hz. Flexible Vinyl tubing with a 1.91-cm inner diameter was attached to the input and output nozzles of the pump head. The 1.91-cm tubing was connected to a 3.18-cm inner diameter tube using a plastic adapter. To simulate retrograde femoral access in the circulation system, a 22F DrySeal introducer sheath (W.L. Gore & Associates) was modified by cutting off the main sheath and soaking the stump in ethanol. The stump was then manually scrubbed with steel wool to remove all coating residue and ensure the port of entry into the flow loop would not be a source of possible polymer contamination in each experiment. The stump was fitted into the 3.18-cm tube at a slight angle to allow for easy placement and minimal friction on insertion of the test sheaths into the flow loop. The treated stump was then secured into the Vinyl tubing using an adhesive externally. The tubing lengths were adjusted to allow for the loop to hold a total of 1 L of fluid and pump effectively at the desired pump rates (Fig 1). Buffered Ringer's lactate (RL) fluid was selected as the test solution because the chemical components and pH most closely resembled that of human plasma. Test runs of the flow loop with distilled water were completed before testing the sheaths of interest to ensure no leaking occurred within the flow loop, resulting in lost sample, and to ensure total and complete emptying of the flow loop was possible.

Sheaths of interest. Six sheaths from each manufacturer of interest were tested, including Zenith Alpha abdominal endovascular stent grafts (Cook Medical), DrySeal sheaths (W.L Gore & Associates), and Sentrant introducer sheaths (Medtronic). Noncoated Check-Flo performer introducer sheaths (Cook Medical) were used as controls. A total of three runs of the control Cook Check-Flo performer introducer sheaths and six runs of each Zenith Alpha abdominal endovascular stent grafts, DrySeal sheaths, and Sentrant introducer sheaths were completed. These were selected because these are the most used devices in our institution for aortic-based endovascular procedures and are believed to be used ubiquitously. The sheaths were not manipulated or prepared in any way before insertion into the flow loop to minimize as many variables as possible that could introduce damage to the tested sheaths. The sheaths were simply unwrapped and inserted into the flow loop immediately.

Sample collection. Before beginning sample collection, the flow loop was flushed with deionized water for 30 minutes at the beginning of each day of runs. This was done to ensure any residual impurities left behind from the previous use of the flow loop had been washed out. Next, the circuit was flushed with 1 L of RL for 30 minutes as a control step before testing each sheath. The control run sample was collected and labeled Flush for analysis. After the Flush run, a fresh 1 L of RL was poured into the

Fig 1. Finalized flow loop holding 1 L of Ringer's lactate (RL) solution.

loop, and the sheath of interest was inserted via the retrograde port.

The total surface area of each sheath inside the system was preset at 341.2 cm^2 based on the smallest, shortest sheath available for testing. Given the variability between the sheaths in the test groups, the length of the sheath inserted into the system was altered to ensure the total surface area for each run was equal. This guaranteed that the same area of polymer coating was exposed in the flow loop for each sheath of interest. The specific details and measurements used to obtain an equal surface area exposed in each run are described in Table I.

The circuit ran for 150 minutes at a simulated cardiac output of 3 L/min. The flow loop was then drained and the fluid collected for analysis, which was labeled the Sheath run. After the Sheath run, the circuit was run for 15 minutes with a new 1 L of RL to rinse the system and remove any residual polymers. This RL was discarded. The circuit was then flushed again with a fresh 1 L of RL for 30 minutes, which acted as the new Flush baseline control run for the next new sheath.

Quantitative and qualitative analyses. The Flush and Sheath run samples were analyzed quantitatively and qualitatively. The quantitative analysis was conducted by weighing the dried and filtered polymer per Sheath run. First, a clean piece of filter paper with a 2-μm pore size was weighed using an analytical balance. After a thorough reconstitution of the collected 1-L Sheath run, 400 mL of the 1-L sample was filtered and dried using vacuum filtration until a solid sample remained. The mass of particulate matter present in the 400-mL sample was then calculated. To control for contaminants in each run, the particulate mass for the Flush run was subtracted from that of the Sheath run to provide the true mass of actual polymer shed from each sheath only. This value was then multiplied by a factor of 2.5 for determination estimation of the particulate matter present in the 1-L samples collected.

$$\text{Sheath run} - \text{Flush run} = \text{Mass of Polymer in } 400 \text{ mL}$$

$$(\text{Mass of Polymer in } 400 \text{ mL}) \times \frac{1000\ mL}{400\ mL} = \text{Mass of Polymer in } 1000 \text{ mL}$$

The qualitative assessment was completed using attenuated total reflectance (ATR) spectroscopy on a Tensor II FTIR Spectrometer (Bruker Optics). Direct samples of each sheath were taken before soaking in the flow loop. These pieces of sheath were then characterized using ATR spectroscopy to provide positive control comparative chromatograms for the samples from the Flush and Sheath runs to ensure that what was measured was truly polymer. ATR spectroscopy of clean filter paper was also completed to account for noise from each sample. The spectra from each sample were compared to the direct samples corresponding to each sheath tested and the clean filter paper spectrum to confirm that the particulate matter present in each of the samples had been shed from the polymer coated sheaths.

Particle size light scattering analysis was performed using a N4 Plus Particle Size Analyzer (Beckman Coulter) to determine the mean ± standard deviation particle size and particle count. Three cuvette samples from each 1-L sample were taken, and the mean ± standard deviation particle size and particle count were used. The average weights and mean particle sizes were derived from pooling all runs from the same manufacturer.

Statistical analysis. Quantitative data are presented as the mean ± standard error of the mean. A comparison of particle sizes between groups was performed using the Student *t* test. Statistical significance was defined as $P < .05$. All statistical analyses were performed using Microsoft Excel (Microsoft Corp).

Table I. Surface area, radius, and length dimensions for experimental and control sheaths

Device	Surface area exposed, mm^2	Radius, mm	Length[a] inserted, cm
Cook control sheath (18F)	3411.66	3.0	18.2
Cook Zenith Alpha device			
18F	3411.66	3.0	18.2
20F	3411.66	3.33	16.3
Gore DrySeal sheath (20F)	3411.66	3.33	16.3
Medtronic Sentrant sheath			
14F	3411.66	2.33	23.3
16F	3411.66	2.67	20.3

[a]Length (mm) = (surface area target based on shortest and smallest sheath fully inserted)/(2 × π × radius of sheath).

Table II. Four different endovascular sheaths tested for particle quantity and particle size

Variable	Cook check-Flo performer introducer (uncoated control)	Cook Zenith Alpha stent graft	Gore DrySeal sheath	Medtronic Sentrant introducer sheath
Particle quantity, mg/L	0.06 ± 0.02	2.87 ± 0.52[a]	1.07 ± 0.06[a,b]	0.98 ± 0.14[a,b]
Particle size, μm	1.6238 ± 0.7252	1.6879 ± 0.6747	0.5631 ± 0.1712	0.4336 ± 0.1896

[a]$P < .05$ compared with control.
[b]$P < .05$ compared with Cook Zenith.

RESULTS

To assess the amount of shedding of polymer coatings from the test sheaths, quantitative analyses were performed (Table II). The amount of shedding was significantly greater for all three sheaths compared with the control sheath. The Cook Zenith Alpha stent graft sheaths showed significantly greater shedding compared with the Gore DrySeal sheath and Medtronic Sentrant introducer sheath. The Cook Zenith Alpha had significantly more residue weight (2.87 ± 0.52 mg/L) compared with the Gore DrySeal (1.07 ± 0.06 mg/L) and Medtronic Sentrant introducer (0.98 ± 0.14 mg/L) sheaths (Table II). No significant differences were found in the shed residue between the Gore DrySeal and Medtronic Sentrant introducer sheaths.

To determine the particle sizes from each sample, the results from the light scattering analyses were evaluated. The mean ± standard deviation particle size for the control sheath and the Cook sheath were similar (Table II). The mean ± standard deviation particle sizes were considerably smaller for the other two sheaths. The Cook sheath had the highest number of particles compared with the other sheaths (Table II).

To confirm that the particles present in the solution were the hydrophilic polymer coating of interest, ATR spectroscopy analysis was performed, and the chromatographs were compared (Figs 2-5). ATR spectroscopy analysis is solely used in identifying and characterizing particulates and not in quantifying the particles. Unique wave numbers are identified, with peaks in the graph correlated with the presence of particulate and not the absolute number of particulates. The ATR analysis of the Cook Zenith Alpha sheath, serving as the positive control, is shown in Fig 2, *A*. The Sheath run after analysis is shown in Fig 2, *C*. These two runs are presented overlapping each other in Fig 2, *D*. In this overlap, a wave number peak is present in both the positive control and the Sheath run, supporting the presence of the sheath particles in the experimental sample. The ATR spectra for the Medtronic sheaths can be seen in Fig 3. A slight peak occurred in the Sheath run (Fig 3, *C*) at the same wave number as that of the positive control (Fig 3, *A*) This similarly confirms that the intensities observed in the Sheath run represent true particles shed from the sheath (Fig 3, *D*, overlap). The ATR spectra for the Gore sheaths can be seen in Fig 4. The Gore DrySeal sheath showed no peak at the expected wave number in the Sheath run (Fig 4, *C*) compared with the positive control (Fig 4, *A*). This is further represented in Fig 4, *D*, because no overlap in the expected peak is shown, indicating minimal shedding not detected by ATR analysis. Finally, Fig 5 shows the ATR spectra for the control sheath. The peaks seen on the samples from the Sheath run (Fig 5, *C*) correlated very strongly with the peaks seen on the samples of the plain filter paper (Fig 5, *B*) indicating that the results from the Sheath runs of the control sheaths revealed minimal shedding. Samples of plain uncoated sheaths still produce an ATR signal (Fig 5, *A*); however, these peaks do not line up with that captured in the true Sheath run (Fig 5, *C*).

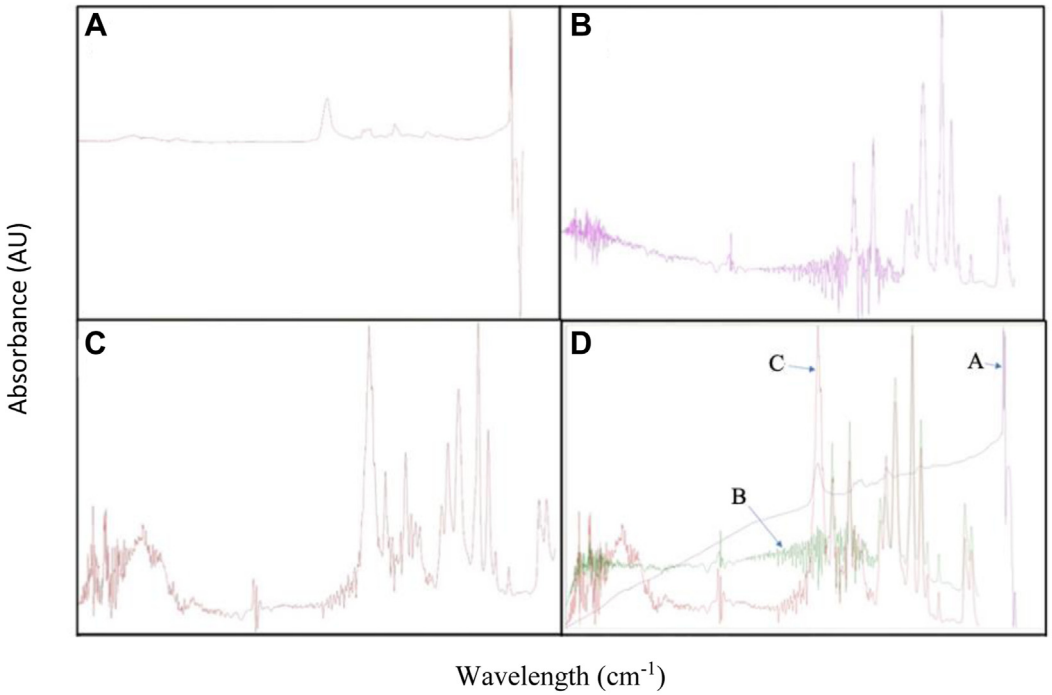

Fig 2. Attenuated total reflectance (ATR) chromatographs of a Cook Zenith Alpha stent graft. **A,** Profile of a small sample cut from the surface of the sheath. **B,** Profile of a blank piece of filter paper. **C,** Spectrum of the dried filter paper from the Sheath run. **D,** Overlay of profiles shown in **A** to **C,** which has been baseline corrected.

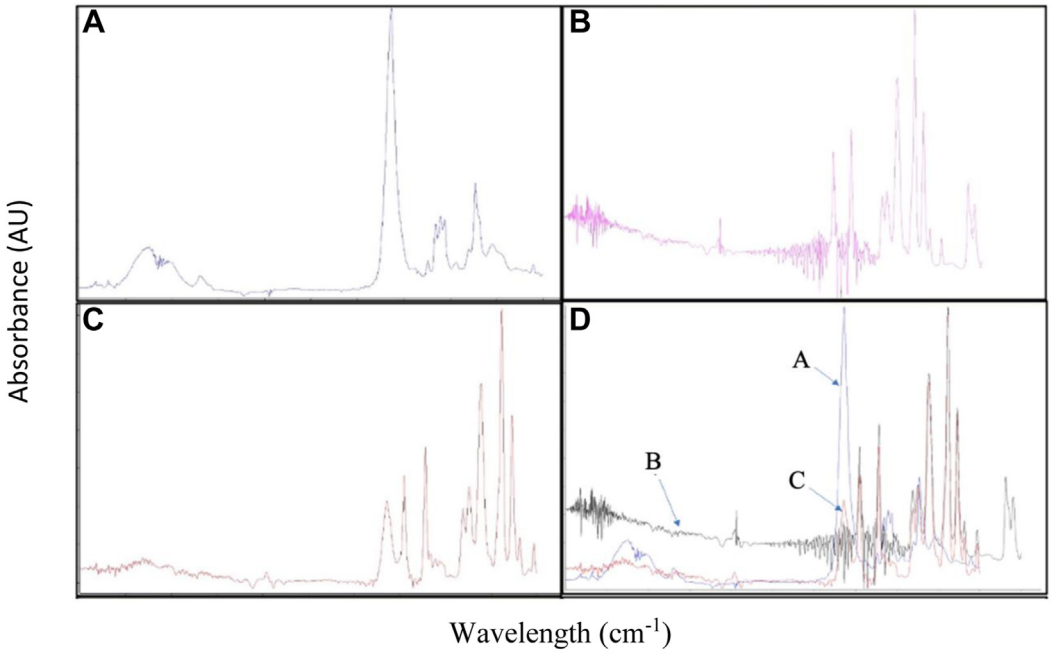

Fig 3. Attenuated total reflectance (ATR) chromatographs of a Medtronic Sentrant introducer sheath. **A,** Profile of a small sample cut from the surface of the sheath. **B,** Profile of a blank piece of filter paper. **C,** Spectrum of the dried filter paper from the Sheath run. **D,** Overlay of profiles shown in **A** to **C,** which has been baseline corrected.

The ATR analysis of the Sheath runs and subsequent Flush runs after each hydrophilic coated Sheath run are shown in Supplementary Figs 1 to 3.

DISCUSSION

Although hydrophilic polymer coatings have improved device and vessel trauma-associated morbidity and

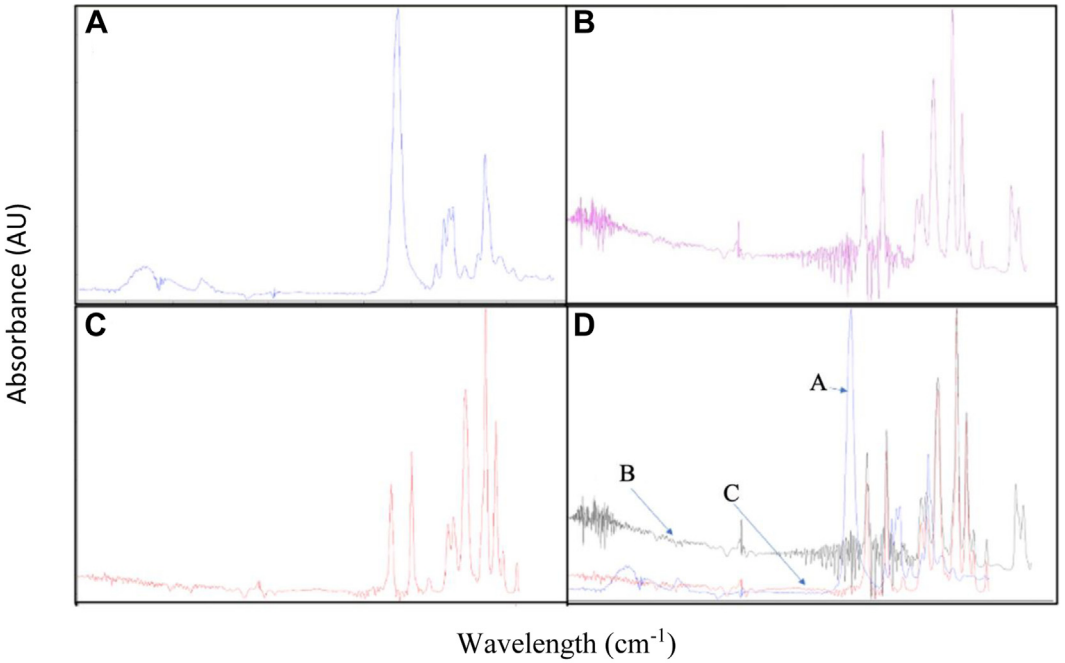

Fig 4. Attenuated total reflectance (ATR) chromatographs of a Gore DrySeal sheath. **A,** Profile of a small sample cut from the surface of the sheath. **B,** Profile of a blank piece of filter paper. **C,** Spectrum of the dried filter paper from the Sheath run. **D,** Overlay of profiles shown in **A** to **C,** which has been baseline corrected.

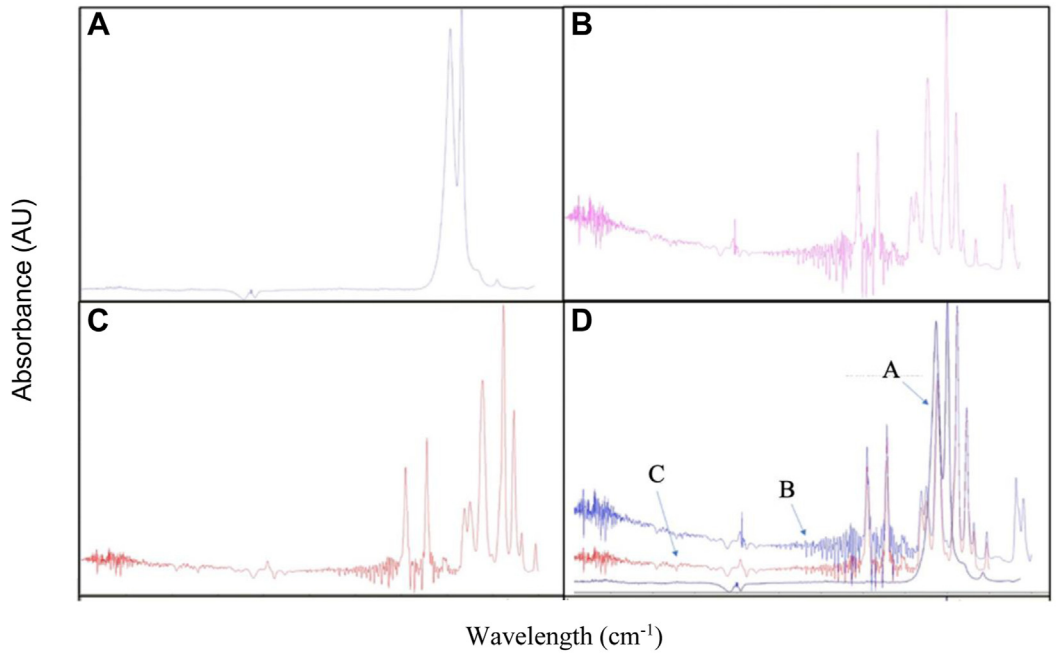

Fig 5. Attenuated total reflectance (ATR) chromatographs of a Cook Check-Flo performer introducer (control) sheath. **A,** Profile of a small sample cut from the surface of the sheath. **B,** Profile of a blank piece of filter paper. **C,** Spectrum of the dried filter paper from the Sheath run. **D,** Overlay of profiles shown in **A** to **C,** which has been baseline corrected.

mortality, HPE has been attributed to various complications, including distal ischemia and, even, death after common aortic and cardiac procedures such as thoracic endovascular aortic repair and transcatheter aortic valve implantation.[6-14] A review of the literature found many case reports of HPE secondary to percutaneous

intervention. However, it is likely, given the broad scope of how this phenomenon presents clinically, that HPE is likely significantly underrecognized and subsequently underreported. Many existing publications are retrospective clinical reports that show histologic hydrophilic material in the heart,[5,8,13] lung,[4,9] and brain[3,8,15] after autopsy. HPE can be identified clinically as distal ischemic skin lesions, renal dysfunction, stroke, respiratory complications, mesenteric ischemia or infarction, and a wide variety of clinical sequelae depending on the location of polymer embolization.[1,4,6-16] Despite the presence of these reports, studies quantifying polymer shedding in the in vitro setting and direct comparisons between products are lacking. In vitro manipulation of a Fastracker-18 infusion microcatheter (Target Therapeutics) produced particulate that shared Gram stain properties found on autopsy in four cases.[17] That study marks one of the first in vitro analyses supporting the presence of HPE and, subsequently, resulted in the discontinuation of the device. Otsuka et al[11] previously reported concerns regarding the polymer layering, citing cracking of the polymer as a potential cause of adverse effects such as local inflammation and thrombosis. This was present in the three commercially available stents they reviewed using scanning electron microscopy. Despite supporting the phenomenology around HPE, to the best of our knowledge, no study has quantified polymer particulates or compared these metrics between popular products.

The results from our in vitro study suggest that hydrophilic polymer shedding occurs with three different Food and Drug Administration–approved endovascular product manufacturers. The quantitative analysis illustrates that Cook Zenith Alpha stent grafts shed significantly more particles than do the Medtronic Sentrant and Gore DrySeal sheaths in a controlled and equivalent environment compared using vacuum filtration and weighing. We found no significant differences in particle shedding or mass between the Gore DrySeal sheath and Medtronic Sentrant introducer sheath.

This is important to understand because it highlights the differences in sheath shedding potential between competitors and illustrates the presence of the HPE phenomenon in a reproducible scenario. Although differences in shedding profiles between manufacturers were present, the differences in clinically relevant sequelae, such as inflammation and vascular occlusion, are unknown. Although we can propose potential complications associated with HPE, we are unable to compare the morbidity of such events between the devices used. However, we believe this is still an important matter to consider.

Regarding the qualitative analysis, our findings showed that the control sheaths and Cook Zenith sheaths have similar particle sizes, and the Gore and Medtronic sheaths have considerably smaller mean particle sizes. The polymer sloughing off the Cook Zenith sheaths was also visually larger than that any of the other sheaths according to the Beckman Coulter N4 plus particle size analyzer. However, this also brings into question the particle sizes of the control sheaths, which do not have a coat and, therefore, should not result in any hydrophilic particle sloughing. It is possible that in the manufacturing of the control sheaths, they could have come in contact with the coating material used for the hydrophilic sheaths assembled in the same facility. This would explain why the mean particle size of the control sheaths is similar to that of the Cook Zenith sheaths and not the other two companies. Furthermore, although not necessarily hydrophilic, almost certainly, some level of particulate matter is present that coats even nonhydrophilic sheaths and is at risk of sloughing off. Alternatively, despite efforts to separate the Sheath runs with copious Flush runs, some particles could have become adherent to our flow loop system, resulting in a baseline cross-contamination. Visually and according to the ATR spectroscopy analysis, no hydrophilic polymer was present in the control solution. Therefore, the reported particles present in the solution were likely a negligible amount, which was further supported by the quantitative analysis. The clinical effects of particle size are also unknown. Although it could be inferred that a larger polymer size would result in larger clinical events, this might not necessarily be the case. We believe it is not so much the embolized particle size but more the quantity of polymer that sloughs off. As evidenced by our own clinical experience, two deaths occurred from the sheer amount of polymer identified in multiple organ beds.[10] Furthermore, the inflammatory reaction resulting from widespread polymer embolization would likely result in a global inflammatory response and significant clinical sequela. Particle size vs particle quantity is an important clinical question not answered by the present study but should be considered for future studies.

Challenges were also encountered in our qualitative determination of polymer shedding. Despite our ability to physically produce a solid sample for quantitative testing in each Sheath run filtrate, it was challenging for the ATR spectroscopy to pick up signals for both the Gore and Medtronic Sheath runs. This discrepancy is believed to be caused by a combination of the small particle size of the polymer and the small count shed from the Gore and Medtronic sheaths, making it difficult for the ATR device to detect the presence of polymer. Moreover, because suction-based drying methods were used for the sample, it is also theoretically possible that a mass of sample was lost in the suction drying process because the pores of the filter paper could have accommodated the particle size. Alternatively, despite thorough mixing of the 1-L sample, the aliquot used did not capture the true amount of solute suspended in the solution. Although laboratory and testing measures were taken to ensure maximum surface area analysis in the

ATR machine, we believe that the small particle quantity and small particle size made it difficult for the machine to detect the Medtronic and Gore sheath polymer. This could account for the lack of peak identified in Fig 4, *C*, compared with the peak in Fig 4, *A*, and the reduced intensity of the peak in Fig 3, *C*, compared with Fig 3, *A*. However, one can theorize that this finding still suggests that both these sheaths produce the smallest and least amount of shedding material, which might be clinically favorable.

Instead of histomorphologic examination such as that used by Stanley et al,[12] our group used ATR chromatographs to confirm that the solute material was shedding from the polymer coated sheaths. Because our analysis method used vacuum filtration and vacuum drying, we opted to use the ATR method to analyze the surface of the filter paper. ATR analysis is a powerful tool for measuring solids.[18] This technique allows light to be reflected off the surface of the dried filter paper, with different types of particulate matter creating different types of reflectance patterns. The main advantage of ATR is that it requires no additional sample preparation and is a quick and accurate method to characterize the presence of polymer on the surface of filter paper. Instead of visual similarity determining the relationship between two samples in a histomorphologic analysis, ATR provides both qualitative and quantitative comparisons because the wavelength peaks of the sheath and Sheath run can be compared directly. This is a novel technique for HPE investigation, with few, if any, groups using ATR for this in the current literature. Future studies interested in determining the specific components or compounds of each polymer coating could use reverse phase liquid chromatography—mass spectrometry to better guide the further design and engineering of sheaths. This would be helpful in achieving a better understanding of the molecular differences between each sheath.

Study limitations. The present study has intrinsic limitations that need to be recognized. The results from this bench top model cannot be directly translated to an in vivo environment. Important features such as blood viscosity, vessel tortuosity, calcific disease, intraoperative medications, turbulent blood flow, and various other physiologic characteristics, all of which could influence shedding, were not mimicked, limiting the translation of these findings to the real-world setting. Second, endovascular cases can range from only a few minutes of sheath exposure to many hours of exposure, which, working under an assumption that the dwell times in circulation will affect the amount of shedding, would influence the possible intensity of sequelae secondary to HPE and the amount of polymer embolized. Because our study only investigated runs of 150 minutes in a flow loop, the conclusion that the amount of polymer shed correlates directly with the time a sheath is exposed to blood flow cannot be made. However, we speculate that the duration of sheath exposure is a likely risk factor in HPE outcomes. To determine this would require future studies in this area comparing shedding at various dwell times. Finally, given the limitations of time and equipment, the entire 1 L of the flow loop sample was not analyzed by ATR for qualitative analysis nor was it fully dried for quantitative analysis, rather a sample were taken. This could have affected the results by not capturing enough polymer sample to result in an accurate reading or weight.

CONCLUSIONS

Hydrophilic polymer embolization is a rare complication that needs more research. Our results have confirmed the presence of HPE in an in vitro model, comparing three commercially available endovascular sheaths. We found that polymer shedding in all three devices was significantly greater than that from uncoated sheaths, with significant differences noted between manufacturers. Hydrophilic polymer coatings have undoubtedly aided in the major advancements of endovascular devices and technologies; however, like most developments, they are not perfect and come at a potential cost. HPE should be considered during product development as manufacturers seek to develop coatings that are more durable and stronger owing to their potentially harmful sequelae. Future studies should also evaluate in vivo outcomes by comparing available devices.

AUTHOR CONTRIBUTIONS

Conception and design: AM, GY, SS, JG
Analysis and interpretation: AM, GY, NR, JC, SS, JG
Data collection: AM, GY, BZ, SS
Writing the article: AM, NR, BZ, SS
Critical revision of the article: AM, GY, NR, JC, BZ, SS, JG
Final approval of the article: AM, GY, NR, JC, BZ, SS, JG
Statistical analysis: GY
Obtained funding: AM
Overall responsibility: AM

DISCLOSURES

J.G. is a consultant for Cook Medical. A.M., G.K.Y., N.R., J.C.C., B.Y., and S.S have no conflicts of interest.

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