Clot accumulation at the tip of hemodialysis catheters in a large animal model

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Abstract

Background: The issue of side holes in the tips of the tunneled cuffed central venous catheters is complex and has been subject to longstanding debate. This study sought to compare the clotting potential of the side-hole-free Pristine hemodialysis catheter with that of a symmetric catheter with side holes.

Methods: Both jugular veins of five goats were catheterized with the two different catheters. The catheters were left in place for 4 weeks and were flushed and locked with heparin thrice weekly. The aspirated intraluminal clot length was assessed visually prior to each flushing. In addition, the size and weight of the clot were recorded upon catheter extraction at the end of the 4-week follow-up

Results: The mean intraluminal clot length observed during the entire study follow-up measured up to a mean of 0.66 cm in the GlidePath (95% CI, 0.14–1.18) and 0.19 cm in the Pristine hemodialysis catheter (95% CI, −0.33 to 0.71), the difference being statistically significant ($p = 0.026$). On average, 0.01 g and 0.07 g of intraluminal clot were retrieved from the Pristine and GlidePath catheters, respectively ($p = 0.052$).

Conclusion: The Pristine hemodialysis catheter was largely superior to a standard side hole catheter in impeding clot formation, and, contrary to the side hole catheter, allowed for complete aspiration of the intraluminal clot.

Introduction

Use of central venous catheters (CVC) in the United States shows little, if any, change in pattern from 2005, with slightly over 80% of patients using a CVC at hemodialysis initiation and 68.5% still using catheters 90 days later, according to the recent data from the United States Renal Data System (USRDS).[1,2] Substantial use of CVCs has also been reported in the European Economic Area (EEA), with studies showing an overall increase in dependency on CVCs for hemodialysis over time.[3–5] Of note, the native arteriovenous fistula (AVF) remains the recommended first choice for vascular access, in both territories,[6–8] due to amore frequent association of synthetic means of vascular access, especially CVCs, with infectious and thrombotic complications. This conception has been repeatedly challenged in the past decade,[9,10] leading the National Kidney Foundation's (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) to recognize the

potential selection biases, both those in favor of the AVF and those against the CVC, as a point of major statistical concern casting doubt on the validity of the previous evidence.[11] Consequently, the KDOQI guidelines restated that the disadvantages of CVC may contribute to poor patient outcomes, but advised that the true magnitude of this effect is not certain in view of the aforementioned selection bias and confounding effects.

Regardless of the type of vascular access, adequate blood flow rate (BFR) is the sanctum sanctorum of hemodialysis, as low BFR extends treatment times and may

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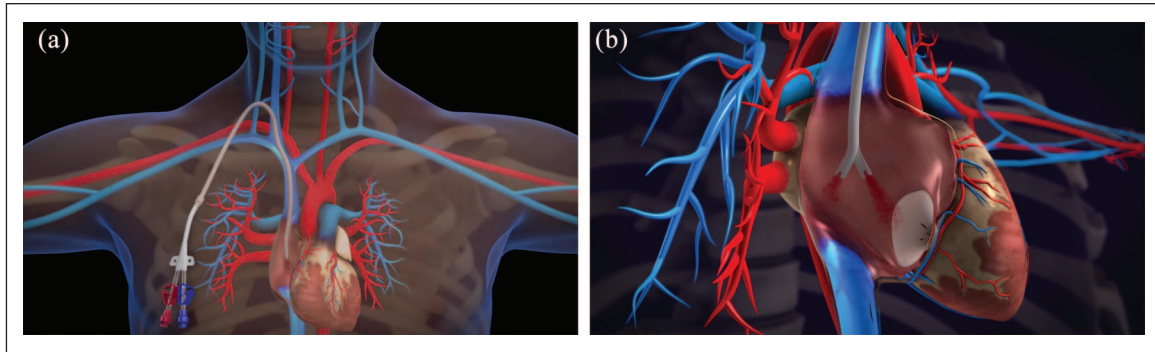Email: mtal@accessmv.com

Figure 1. Pristine hemodialysis catheter tip orientation in the right atrium: (a) anterior-posterior view and (b) lateral view.

result in underdialysis.[6] The most likely cause for a low BFR achieved with CVCs is thrombosis of the catheter, accounting for access loss in 30% to 40% of patients.[6] Somewhat paradoxically, distal side holes, frequently introduced in CVCs with the goal of supporting inflow in case of thrombotic obstruction of the end hole,[12] have been themselves implicated in promotion of thrombosis by serving as anchors for irretrievable blood clots.[13]

The Pristine hemodialysis catheter has a split, symmetrical, side-holes–free tip. It was designed with the anatomy of the right atrium in mind. The placement of the Pristine is such that the tip should be placed in the upper right atrium and is oriented in the anterior posterior position (Figure 1). This catheter design would appear to have a theoretical advantage in diminishing the risk of thrombosis. We devised this study to translate the aforementioned theory into practice by assessing the by-design potential advantages of the Pristine hemodialysis catheter in vivo.

Methods

Animals and experimental setup

Five domestic goats (female; 55–78 kg) were used in this study. Animals were allowed free access to food until 24 h before the procedure, at which time access to food was denied. Water was provided ad libitum until 24 h before the procedure. Before the procedure, animals were sedated with intramuscular ketamine 10 mg/kg + xylazine 0.1 mg/kg, and intravenous midazolam 5–10 mg; intubated and connected to a mechanical ventilator. Anesthesia consisted of 1–2% isoflurane. Tunneled cuffed double-lumen CVCs were inserted in both jugular veins of the animals according to the instructions for use (IFU) provided by the catheters' manufacturers. Pristine hemodialysis catheters (15.5 F polyurethane; Pristine Access Technologies Ltd., Tel Aviv, Israel; hereinafter called Pristine) and GlidePath Long-Term Dialysis Catheters (14.5 F polyurethane; Bard Access Systems, Inc., UT, United States; hereinafter called GlidePath) were evaluated in this study. Catheter right-atrium
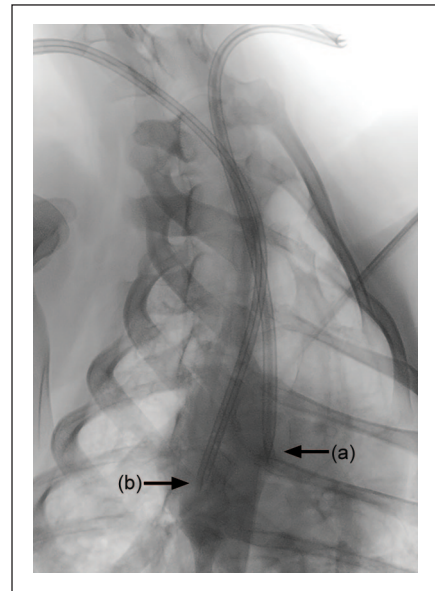

Figure 2. Fluoroscopy imaging of Pristine and Glidepath catheters implanted in the right atrium: (a) Pristine tip and (b) Glidepath tip.

location post-insertion was validated by fluoroscopy (Figure 2). Catheter patency was assessed by the operating physician using a 10 mL syringe with normal saline. At the end of the procedure, animals received a subcutaneous injection of 1 mL/kg of procaine penicillin G 200 mg/mL + dihydrostreptomycin sulphate 250 mg/mL. In addition, cefazolin (2–2.5 g) and dipyrone (1 g) were administered intravenously.

Dialysis treatment imitation

For each imitated treatment, 5 mL were aspirated from each catheter lumen using a syringe with Luer port. Where aspiration was not possible, 20 mL of normal saline were injected to restore lumen patency. Following aspiration, the syringes were checked for clots, findings were documented, and a digital image was taken. The lumens were washed with 20 mL of normal saline and locked with

5000 U/mL of heparin solution diluted according to the priming volume indicated on the catheter.

Follow-up termination and catheter removal

Following completion of the study follow-up, catheter location was assessed using fluoroscopy. Catheters were then aspirated and removed according to the respective IFU. Where a clot residue was still present in the lumen, it was manually retrieved with tweezers by the same operator who aspirated and removed the catheters. The aspirated and the manually removed clot substances were weighed on analytical scales.

Euthanasia

Animals were euthanized with an injected barbiturate (pentobarbital) overdose, in agreement with the American Veterinary Medical Association (AVMA) acceptable method for euthanasia of fully anesthetized small ruminants.[14] Death was confirmed by the animal facility veterinarian after assessing heartbeat, respiration, and pupillary response to light.

Statistical assessment

Both the follow up and end of study results were analyzed using a repeated measures ANOVA model in order to compare the catheters with respect to clot length and weight (total intraluminal clots, aspirated clots, and clot residues). This was done in order to take into consideration the within animal correlation between measurements using the two catheters as well as lumen size (arterial and venous).

Results

Ten tunneled cuffed double-lumen central venous catheters (five—Pristine and five—GlidePath) were inserted in the jugular veins of five animals. Insertions were uncomplicated and uneventful. The two catheters were inserted in each animal, one on each side.

During the 28-day follow-up, imitated treatments were administered three times a week, on Sundays, Tuesdays, and Thursdays. Aspirations from both catheter types were uneventful at all locations. The mean intraluminal clot length aspirated before each session during the entire study follow-up measured up to a mean of 0.66 cm in the GlidePath (95% CI, 0.14–1.18) and 0.19 cm in the Pristine hemodialysis catheter (95% CI, −0.33 to 0.71), the difference being statistically significant ($p=0.026$; Table 1).

None of the animals showed clinical signs of infection during the entire duration of the study. All catheters were removed at the end of the follow-up. The total intraluminal clot weight for a single lumen was calculated by combining the weight of the clot aspirated from the lumen before catheter removal with that of the residual clot retrieved manually immediately thereafter (Figures 3 and 4). This

Table 1. Average intraluminal clot length.

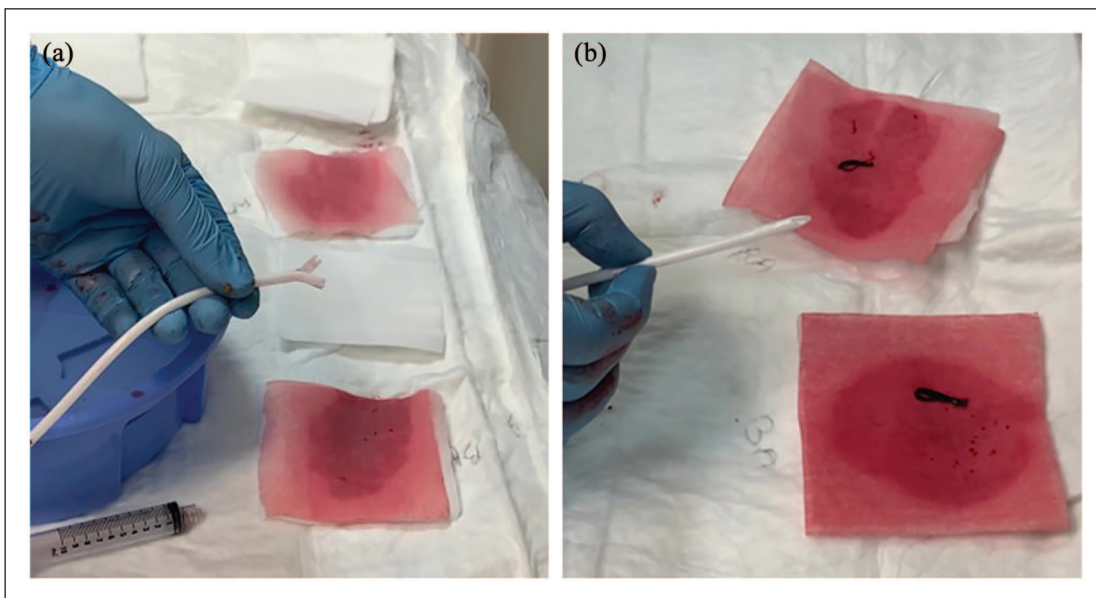| Animal no.	Pristine	Glidepath
830	0.195	0.272
14761	0.190	1.25
5067	0.563	1.318
5321	0	0.454
5128	0	0.009
Total	0.19	0.66

Figure 3. Catheter tips and aspirated clots after 28 days: (a) Pristine and (b) Glidepath.
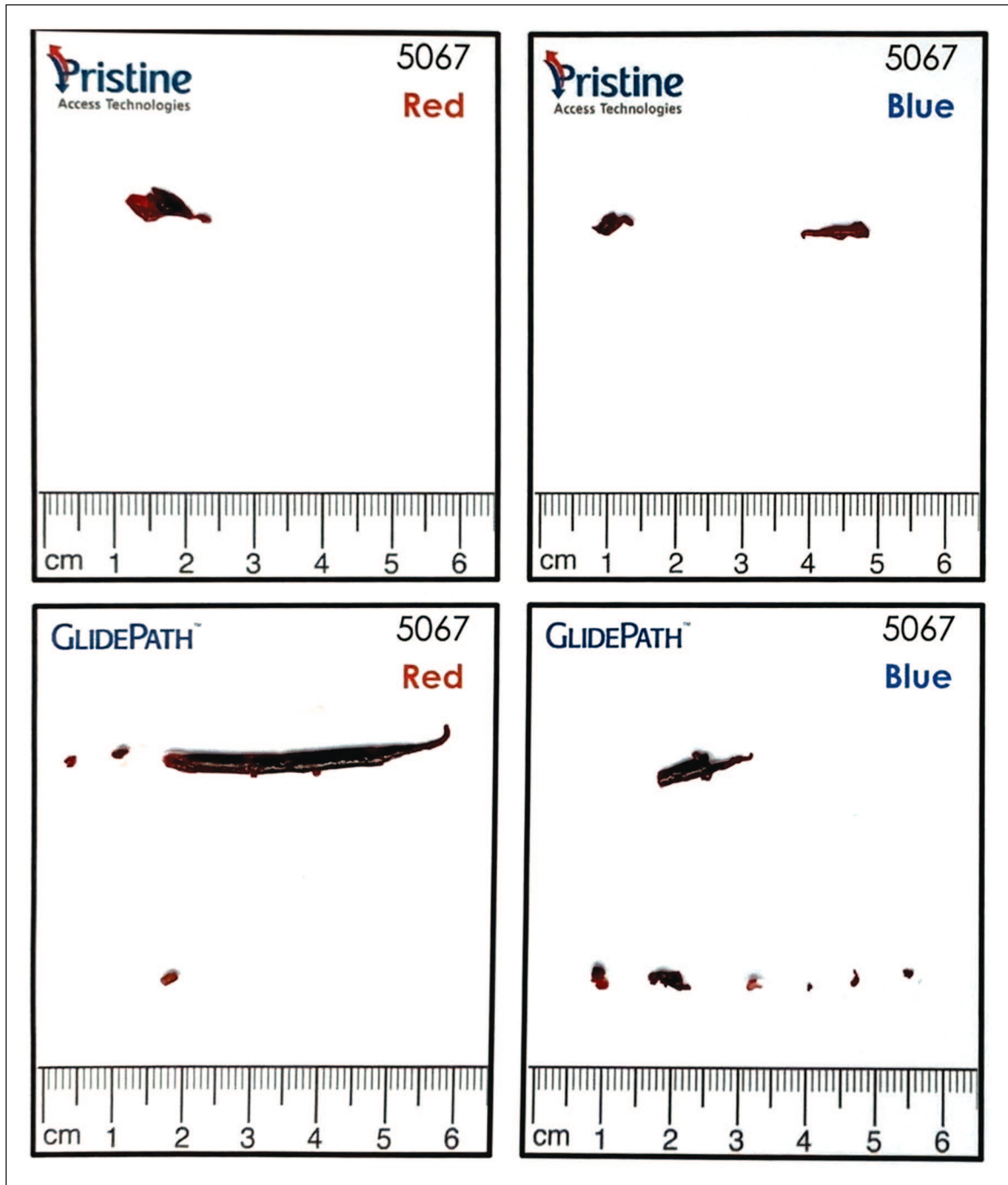
Figure 4. Intraluminal clots removed from Pristine (top) and Glidepath (bottom) tips after 28 days.

reached the mean of 0.0054 g and 0.0372 g for the lumens of the Pristine and GlidePath catheters, respectively, accounting for a mean intraluminal clot weight of roughly 0.01 g per each Pristine and 0.07 g per each GlidePath catheter (Figure 5). Aside of the obvious significance of the overall clot load, one determinant deserves a special consideration. Specifically, residual clot was not detected at all in the Pristine catheters after aspiration, while a mean of 0.002 g of clot were retrieved from the GlidePath

catheters mechanically, following removal of the catheters from the blood vessels.

The almost seven-fold total intraluminal clot weight difference between the catheter types showed a trend toward statistical significance ($p = 0.052$). The differences between the mean weights of the aspirated and manually retrieved residual clot showed the same trend when analyzed separately ($p < 0.09$ in each of the separate analyses). Finally, the mean aspirated, residual, and total intraluminal clot
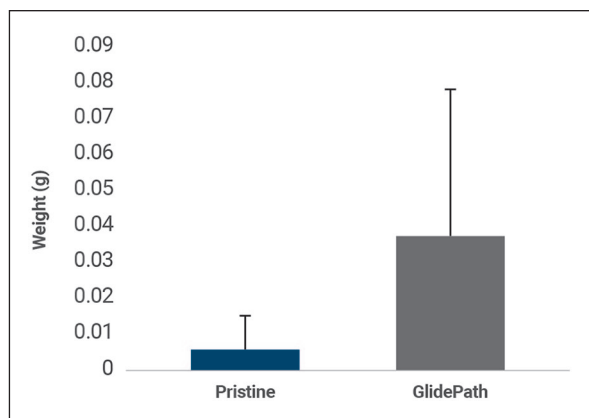
Figure 5. Comparison of total intraluminal clot weight (aspirated + manually retrieved following catheter removal). Data are presented as a mean ± standard deviation for a single catheter.

weights were statistically different from 0 for the GlidePath ($p = 0.03$), but not for the Pristine catheters ($p > 0.64$).

Although this work featured only a limited number of animals observed over a relatively short period of time, the number of clot length observations obtained was considerable. The results of weight evaluation at the end of the study followed suit, showing that the Pristine hemodialysis catheter was not inferior to the Glidepath in any test, while showing superiority to the latter in some. Overall, this reduces the likelihood of study results being significantly affected by a random error.

Discussion

From the data available in USRDS, at 90 days after the initiation, 68.5% of patients are still using catheters.[1] Among prevalent hemodialysis patients in 2018, catheter use was much higher (52%) for hemodialysis patients ≤21 years old (versus 19–21% in other age groups), underscoring the need for a durable vascular access.[2]

Catheter failure due to low BFR or occlusion will likely occur at some time during catheter use, with timing of such occurrence governed, to a certain extent, by the definition of failure. Catheter performance parameters proposed by the NKF Vascular Access Work Group in 2006 mostly relied on the dialyzer BFR achieved, factored by the pre-pump arterial limb pressure.[6] These guidelines were comparable to those issued by the Society of Interventional Radiology,[15] American College of Radiology,[16] and a joint committee of several surgical societies.[17] Dialyzer-delivered blood flow rates greater than 300 mL/min, factored by pre-pump pressure, were an absolute requirement. Noteworthy, in Europe, blood flow rates less than 300 mL/min were used, conditioned on longer dialysis treatment durations.[18] Still, 300 mL/min was a conservative value in the adult practice, and the existing European guidelines referred, and still do, to blood flow of 300 mL/min

available for hemodialysis as the parameter of adequacy in hemodialysis efficiency assessment, despite providing a definition for catheter dysfunction different from their American counterparts.[7,8] The 2019 update of NKF KDOQI guidelines reassessed this definition in view of the accumulated evidence, removing the 300 mL/min requirement.[11] Still, failure to maintain the prescribed extracorporeal blood flow required for adequate hemodialysis without lengthening the prescribed HD treatment is at the core of expectations from CVCs, as it is with any other type of vascular access.[11] Consequently, susceptibility of CVCs to thrombosis remains the principal concern associated with their use. Further, aside of the obvious impact on BFR, thrombosis has been acknowledged as a major predisposing factor in the development of CVC-related infections due to its role in promotion of adherence of bacterial and fungal organisms to catheters.[19–21] This eventually results in catheter-related septicemia[22] and frequently leads to catheter removal, a point where safety and efficacy outcomes converge.

Catheter patency considerations are at heart of the CVC-related research and development. While the shaft design issues of the long-term catheters have been satisfactorily resolved with introduction of CVCs featuring a D-shaped lumen in the mid-body,[23–27] medical device manufacturers still struggle with optimization of the tip of the catheter. Shape-wise, symmetry of the tip showed benefits in preventing recirculation compared to other configurations, such as staggered tips, especially when arterial and venous blood tubing are reversed.[28] Much controversy surrounds the need for side holes which, despite their purpose to support catheter patency,[12] may predispose for thrombus formation by facilitating quick removal of anticoagulant lock solutions by blood flow.[24,29,30] In a computational fluid dynamics analysis, distal side holes present as a low-flow zone with increased clotting risk at the catheter tip.[31] Finally, creation of side holes is riddled with imperfections of the cut surfaces, to which thrombi have been shown to attach firmly and irretrievably.[12,13]

The GlidePath catheter is a double D catheter introduced into practice a decade ago. Admixture of the arterial and venous blood in this catheter is reduced through introduction of curved distal apertures on opposing sides of the catheter. The GlidePath's tip symmetry is incomplete due to a guidewire aperture at the distal tip, as part of the venous lumen, and the offset side holes. Still, in computational analysis, percentages of blood moving out of the catheter from the distal lumen and flow rates through the side holes of Glidepath were similar to those of the original symmetrical catheter, the Palindrome (Medtronic, MN, USA).[32] In that computational analysis, the most prominent flow stagnation regions were detected around side holes and terminal apertures, where laminar flow from the catheter tip is interrupted by inflow from the side holes.[32]

The Pristine hemodialysis catheter is a dual-lumen CVC with a double-D–shaped cross-section of the mid-shaft.

Unlike GlidePath, it has a pre-formed short symmetric split-tip and is devoid of side holes. In our study, despite having a diameter slightly larger than that of the comparator, the Pristine hemodialysis catheter was largely superior to GlidePath in impeding clot formation, as evident from a significant reduction in the clot length and from the trend toward reduction in the clot weight. In addition, contrary to GlidePath, the Pristine hemodialysis catheter allowed for complete aspiration of the intraluminal clot. The ability to retrieve the clot without removing the catheter is an important prerequisite of durable patency of CVCs, and, as noted earlier, a significant contribution to the safety of its use, through reduction of catheter-related septicemia. Aside of the obvious benefit to the patient stemming from the durable vascular access patency, this quality is likely to contribute to reduction in the frequency and duration of use of antibiotics, which, in turn, will contribute to the effort of reduction of spread of antibiotic resistance.

Declaration of Conflicting Interests

Funding

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