1. Introduction

Despite the emphasis on arteriovenous fistula creation in patients requiring renal replacement therapy, catheter-based hemodialysis remains a valuable access option that allows for immediate initiation. They continue to serve as an important option for chronic kidney disease (CKD) patients who are: (a) awaiting a permanent AV access creation or maturation, (b) in need of acute hemodialysis, (c) have exhausted traditional access routes, and (d) those suffering from graft infection or extravasation episodes [1].

Catheter-related sheath (CRS) formation, previously referred to as the “fibrin sheath” is a well documented physiologic reaction occurring between the catheter, vein wall, and blood elements. The incidence of central venous CRS formation is reported to occur in 42%-100% of central venous catheters [2-5]. The sheaths can be asymptomatic or result in a number of complications including withdrawal occlusion, medication extravasation, thrombosis, infection and in rare cases pulmonary embolism. Repeat catheter removal and replacement, or loss of an access route is not infrequently the end result of catheter related sheath formation. It is important for those clinicians caring for CKD patients to be aware of the clinical and imaging manifestations of CRS and understand the interventions that can be used to mitigate them.

The goals of this chapter are to review the existing literature on CRS in animals and humans, to provide a current, coherent explanation of the composition of the CRS and how they form, and describe the clinical manifestations and treatment options that are available.
2. A brief history of central venous catheters and catheter-related sheaths formation

The first catheterization of a central vein was performed in 1733 by an English clergyman named Stephen Hales who fixed a glass tube to the left jugular vein of a mare to measure venous pressure [6,7]. It wasn’t until the late 1920’s that Werner Forssmann performed the first documented central venous catheterization in a human when he passed “a well oiled 4F ureteric catheter” through his left antecubital fossa and into this heart. Remarkably, Forssmann then climbed several flights of stairs to the x-ray department to visualize his catheter placement [8,9]. Decades passed and it was not until the 1970’s that the central venous catheter became widely available [10].

One of the earliest descriptions of CRS covering a central venous catheter described a “fibrin sleeve” published in the French literature in 1964 by Motin [11]. A number of subsequent studies referred to the central venous catheter related sheaths as a fibrin sleeve and fibrin sheath [2,3,5]. More recently, the work of Xiang et al. more accurately described the CRS as cellular-collagen tissue covered by an endothelial layer. Fibrin was described a component of an early physiologic response to the catheter that consists of pericatheter thrombus, but the CRS itself is not composed of fibrin [12]. Subsequent papers by these authors and others reinforced the concept of CRSs representing a spectrum of thrombosis and thrombus organization [13-16].

3. Clinical implications

The most common manifestation of CRS is catheter dysfunction. This interrupts the patient’s medical therapy, may require intervention ranging from thrombolytic infusion to catheter removal or exchange, and may have long lasting implications such as loss of specific venous access locations. Extravasation of fluids or intravenous medication is a less common but certainly significant complication that can result in tissue loss and necrosis. Thrombus that forms on the CRS or the CRS itself can on rare occasion become dislodged and embolize to the pulmonary circulation. Finally, there have been reports that the presence of the sheath is a risk factor for catheter-related bacteremia and infection.

When dysfunction is present, the patient is commonly referred for radiographic evaluation of the catheter. A radiograph or fluoroscopy of the chest is performed to document catheter tip position. Contrast injection of a normal, functioning catheter should show contrast exiting the end-holes and filling a substantial portion of the vein lumen distal to the catheter tip. When a sheath is present, contrast will track in a retrograde fashion along the catheter. The contrast will then “spill” out into the vein lumen via gaps or fissures in the sheath.
Figure 1. Catheter injection under fluoroscopy. The existing catheter has been pulled back approximately 10 cm and then injected. Contrast fills a well developed sheath considerably narrower than the expected diameter of the superior vena cava. A guide wire has been advanced through the other catheter lumen and is positioned in the inferior vena cava in preparation for exchange.
4. Histopathology of catheter related sheaths

By the middle of the 20th century, central venous catheters were being placed with subclavian and jugular approaches and used for intravenous infusion [6]. The presence of a tissue-like covering was reported after catheters had been indwelling for relatively short periods of time. An early description of this coating appeared in the French literature in 1964 [11]. Since that time, the covering has been referred to as a fibrin sleeve [2,3], a sleeve thrombus [4], a sleeve [12], and—the most recognized phrase—a fibrin sheath [5]. The reported frequency of this observation ranges from 42% to 100% [2-5]. Although there are a number of articles in the literature that are concerned with the clinical aspects of CRS; a minority of these focus on the sheaths’ histopathologic features and microscopic development.

An often-referenced article [2] describes the findings at autopsy in 55 patients with subclavian vein catheters. In that study, sheaths were identified in all specimens, even as soon as 24 hours after catheter insertion. Microscopic evaluation was reported to reveal a predominately fibrin makeup, “with no evidence of endothelialization or organization.” The sleeve was observed, in many cases, to be adherent to the adjacent vein wall.

Well into the 1990s, descriptions of a catheter-related sheath consisting of “fibrin and thrombocytes” [17] or a “layer of investing fibrin and proteinaceous material” [18], could still be found in the literature.

Later, two reports offered a more detailed microscopic and histologic description. In 1996, a study [19] was performed in which small-caliber silicone catheters were inserted in 15 rats. The catheters were placed via a jugular approach, and the animals were sacrificed at 3, 7, and 60 days. Catheter-related thrombus, with points of attachment to the vein wall, was observed in the earliest group. The thrombus underwent changes typical of organization at the 7-and 60-day observation points and evolved into what was described as a “dense fibrous connective tissue containing numerous spindle-shaped fibroblasts” [19].

In a second, larger study [12], again performed in a rat model, catheters were placed via the jugular vein in 123 animals. Histologic changes were studied at catheter indwelling times that ranged from 1 day to 6 months. A true pericatheter thrombus was identified in all animals within the first 3 days after catheter insertion. A transformation occurred from pericatheter thrombus to a more cellular structure composed of collagen with smooth muscle and endothelial cells; this latter structure appeared 1–4 weeks after catheter placement.

Three kinds of catheter-associated thrombus have been described [14]. The first variety is a mesh-like thrombus that bridges the vein wall and catheter. This is thought to evolve into the mixed cellular and collagen catheter-related sleeve described by these authors in an earlier report [12]. A second, nonorganized form of thrombus has been termed “sleeve-related thrombus” and is found on the distal aspects of the indwelling catheter itself. This variety has no attachment to the vein wall and is histologically and physically separate. Last, mural thrombus is found on the vein wall adjacent to the distal intravascular aspect of the catheter. This thrombus undergoes organization and is thought to become incorporated into the vein wall. It is uncertain why a thrombus at a particular location develops into a cellular bridge instead of incorporating into a vein wall, although catheter motion may influence this process [20].
In a large animal model (swine), Forauer et al [16] examined CRS formation at 7, 14, 30, and 45 days after catheter insertion. This confirmed the cellular nature of the sheath including endothelial and smooth muscle cells; see Figure 3. These cell populations were not randomly present; the smooth muscle cells assumed a typical orientation to the vessel lumen with the long axis of the cell oriented with the circumference of the vessel. The smooth muscle cells were also involved in neovascularity of the sheath, forming small lumens lined with endothelial cells. The endothelial cells formed a monolayer covering the external portion (vascular lumen aspect) of the sheath that was indistinguishable from adjacent vein wall intima.

The development of the catheter-related sheath is postulated to begin with thrombus that develops after trauma associated with the catheter insertion procedure [3,21]. Local trauma occurs at the venotomy site. Factors contributing to thrombus formation include disturbance of normal flow through the venous segment and stasis that occurs between the catheter and the vein wall. Other locations of trauma occur at foci of friction of the catheter against the vein wall or catheter tip impact against the vein wall and in segments where catheters lie in acute angles within the course of the vein [20,21]. In addition, acute or chronic (organized) thrombus has been confirmed in catheter stripping specimens [13].
The role of catheter-tip trauma and associated thrombus formation has been examined, also in a swine model [20]. Silicone catheters with or without a 0.018-inch wire stabilizing loop at the distal indwelling tip were inserted, and their tips were positioned in the distal aspect of the superior vena cava. In the group in which catheter tips were stabilized by the wire loop, there was only a mild increase in vein wall thickness without vein wall thrombus. In the control group (without the stabilizing loop), mural thrombus formed at the site of local vein wall trauma caused by catheter tip motion. This thrombus subsequently underwent organization and resulted in vein wall thickening and intimal hyperplasia. The organization of intravascular thrombus involves an infiltration by smooth muscle cells and the development of a vascularized connective tissue that includes collagen, smooth muscle cells, and endothelial cells [22,23]. Inflammatory cells are also known to be involved in venous thrombosis [24].

The process of catheter-related sheath formation is a dynamic and ongoing response of the components of the vein wall to the catheter and associated thrombus. The sequence of the steps of sheath formation is similar among animals and humans. Inflammatory, endothelial, and smooth muscle cells are involved in this response, and these are all biologically active cell types. Findings support the hypothesis that a pathologic process occurs when thrombus organizes adjacent to a synthetic scaffold—a catheter. This process differs from intravascular...
thrombus formation because the presence of the catheter within the vessel lumen allows the process to continue with only limited focal vein wall contact.

The role of medical comorbidities, such as diabetes mellitus and hypercholesterolemia, in the formation of CRS has not been well evaluated. A small randomized study evaluating the occurrence of late malfunction in tunneled hemodialysis catheters did note a trend toward late catheter malfunction (either thrombosis or CRS formation) in patients with diabetes, but this did not reach statistical significance ($p=0.054$) [25]. Several series focusing on peripherally inserted central catheters and non-tunneled internal jugular central venous catheters have shown no clear relationship between diabetes or hypercholesterolemia on thrombotic complications [26-28]. The specific role of hypercholesterolemia in CRS formation has not been addressed.

5. Clinical manifestations of the CRS

While this process can remain clinically silent, there are many clinically important sequelae to sheath formation. These include withdrawal occlusion, total occlusion of the catheter [29], vein thrombosis [4,17,30,31], infusate extravasation [30], pulmonary embolus at catheter removal [2,4], and predisposition to infection [32-34]. Vessel thrombosis can also result in loss of the venous access route- a sobering prospect for a patient requiring long-term renal replacement therapy.

The first indication that a CRS is present is often the ability to flush or inject, but the inability to aspirate from a catheter, termed withdrawal occlusion. This occurs when a CRS encases the tip of a catheter and effectively forms a one-way valve [35]. Additionally, defects or rents in the CRS may allow infusion while not providing sufficient area to aspirate; see Figure 1. This persistent withdrawal occlusion results in chronic catheter dysfunction and poor flow rates. It can also result in the serious complication of medication extravasation [36]. Medication extravasation can result in significant morbidity with administration of chemotherapeutic agents. The infusate injected into the catheter exits the end-hole, tracks retrograde between catheter and the sheath and can follow this path back to the venotomy and into the soft tissues; see Figure 4. The patient may experience pain, inflammation, and tissue necrosis.

The thrombotic complications of pericatheter thrombus formation resulting in a catheter related sheath can lead to stenosis or frank occlusion of the veins anywhere along the indwelling path of the catheter. Intraluminal and mural thrombosis may also contribute to catheter dysfunction and complete venous thrombosis. The catheter dysfunction secondary to intraluminal thrombosis may also present with persistent withdrawal occlusion secondary to a “ball–valve” effect within the catheter lumen [37], and may likely manifest resistance to antegrade flushing as well. Mural thrombi may partially or completely block a vein and are often asymptomatic, but may present with arm, neck, head or jaw pain, numbness of the ipsilateral extremity, erythema, phlebitis or venous distension [37]. In the extreme, the patient may display symptoms of superior vena cava syndrome.
Figure 4. Catheter-related sheath causing soft tissue extravasation. a) Early and b) late images from a contrast injection of a right sided chest port. No contrast is observed exiting the distal end-hole of the post catheter. The contrast tracks retrograde along the catheter and exits in the soft tissues of the neck at the level of the venotomy.
CRS and pericatheter thrombus has also been implicated as a risk factor for infection. Mehall et al. established that CRS significantly enhanced catheter related infection and bacteremia. It was postulated that the sheath provides a surface for bacterial attachment and source of septic emboli [34].

Cases of CRS being dislodged into pulmonary vasculature have been described [4,38]. However, this complication appears to be rare or clinically insignificant given the relatively small volume embolic burden and the bridging of cellular tissue with the vein wall.

6. Clinical interventions and management

6.1. Thrombolytic therapy

An initial, conservative approach to patency restoration is the use of thrombolytic agents. Thrombolytic therapy for treatment of hemodialysis catheter malfunction due to thrombosis or CRS has been used for decades. Two basic protocols have been employed: indwelling (“lock”) catheter treatments and infusion therapies. Indwelling or “lock” treatments involve administration of a volume of thrombolytic agent which only fills the catheter lumen for a variable amount of time. Infusion treatments involve the infusion of variable doses of thrombolytic through the hemodialysis catheter over several hours.

Multiple different thrombolytic medications have been used with the two methods above in varying doses over the years. Urokinase was the agent of choice for both protocols until its withdrawal from the North American market in 1999. It was reintroduction to the market in 2002. To date, it is the only thrombolytic agent to be directly compared with percutaneous catheter related sheath stripping (PCRSS) in a prospective randomized trial. In 2000, Gray et al found no significant difference in primary patency between urokinase infusion and PCRSS [39]. Low dose (5000 to 9000 units) indwelling treatments have had mixed results in the literature with successful return of catheter function ranging from 14% to 95% [40]. More recently, positive results with high dose urokinase (25,000 to 100000 IU) indwelling treatments have been reported by Donati et al with recanalization rates up to 100% [41].

Since urokinase was withdrawn from the market in North America, several other thrombolytic agents have been evaluated. Multiple published reports and a clinical trial have shown alteplase to be effective and safe [42-45]. There is evidence that alteplase yields similar or better results compared to UK [46-48]. Although less studied, reteplase has also been shown to be safe and effective but no direct comparison has been made to the more commonly used thrombolytic agents [49,50]. Tenecteplase has also been shown in Phase III trials to be safe and effective in the treatment of dysfunctional catheters [51,52]. Newer thrombolytic agents such as recombinant-urokinase, afimeprase, and anistreplase are currently under investigation [53].

Because the composition of the CRS has a significantly cellular component, the efficacy of thrombolytics must be attributed to interaction with the associated thrombotic elements that are present.
6.2. Percutaneous CRS stripping and other mechanical interventions

Mechanical interventions have also been employed as a treatment for CRSs which result in occlusion or decreased blood flow rates. Such interventions include catheter exchange and PCRSS with balloon disruption. Although sheath stripping is used less frequently in favor of catheter exchange at many institutions, an understanding of the technique is important.

Treatment of occluded central venous catheters by some method of mechanical disruption has been described in the literature as early as 1983 using a straight guide wire advanced through the catheter lumen via a Y-valve under simultaneous constant suction with 100% success [54].

In 1995, Knelson et al [55] described two techniques (a wire only and separate snare technique) for PCRSS. Eleven of the patents had either a J-tipped wire or tip-deflecting wire advanced through the catheter until the curved tip just excited the catheter end, after which it was rotated several times until contrast injection under fluoroscopy demonstrated patency. Alternatively, a snare technique was employed via right femoral vein access. Here, a nitinol loop snare was advanced 5cm over the catheter with the aid of a 6-F guiding catheter, closed and retracted under moderate tension stripping off the sheath surrounding the catheter. Nineteen of the twenty treatments were successful with a mean duration of satisfactory function following intervention of 150 days.

Subsequent retrospective studies have reported high technical success rates [56-59], but with less promising durable clinical results with 45% and 28% primary patency at 3 and 6 months respectively [58]. A study specifically evaluating HD catheter flow rates post stripping yielded more disappointing results: the average flow rate fell below host the institution’s standard by the fifth hemodialysis session [56]. Suhocki found primary and secondary mean patency at 3 and 4.5 months respectively [59]. Johnstone found at 6 months primary and secondary patency rates of 40% and 60%, respectively [60]. In 1999, Brady et al [61] prospectively found median post-stripping patency of 89 days(i.e., 3 months).

In 2007, Reddy et al [62] described a new “internal” snare approach as opposed to the “external” approach from a femoral vein. Here, a nitinol wire was bent in its mid portion 180 degrees resulting in a loop. The loop was then advanced through the proximal lumen until and then was tightened down on the distal portion of the catheter snaring it. The looped nitinol wire was also advanced though the distal lumen. Multiple passes were made in each lumen often resulting in clot/sheath removal. Disruption of the CRS was attributed to two mechanisms of action: the stripping action of the snare over the distal lumen and the deformation/expansion of the catheter as the snare is advanced. Nine internal snare procedures were performed in seven patients who had failed pharmacologic lysis with 100% technical success. With the internal snare procedure, there was a 100% patency at 8 weeks and a mean patency of 108.5 days without complication.

In 2002, Angle et al [63] published a five year retrospective analysis of 115 patients with 340 tunneled hemodialysis catheter fluoroscopic evaluations of which underwent one of five interventions: conservative management (aspiration/flushing), tip-deflecting guide wire manipulation, catheter exchange, PCRSS with a snare via femoral approach, and thrombolytic...
infusion. Failure rates at 30 days using the five management strategies above ranged from 24% to 62%. PCRSS had the lowest 30 day failure rate of all the methods evaluated.

There have been two prospective trials comparing the effectiveness of different techniques on the dysfunctional dialysis catheter. In 2000, Merport et al [64] performed a randomized prospective clinical trial comparing the effectiveness of over-the-wire catheter exchange versus PCRSS over 37 encounters in 30 patients with malfunctioning hemodialysis catheters which demonstrated 1-month patencies of 93% and 31% respectively. Estimated costs were lower in the catheter exchange group.

In 2000, Gray et al [39] performed a randomized prospective clinical trial comparing the effectiveness of PCRSS with a femoral snare approach versus 250,000 U urokinase infusion over 4-hours. Forty-five day primary patency rates for PCRSS and urokinase infusion were 35% & 48% respectively and were not statistically significant (p=.2).

6.3. Other alternatives

Hemodialysis catheter exchange with or without CRS balloon disruption with has been well described with comparable or improved outcomes compared to PCRSS [64-68]. This procedure is performed by placing guide wires through the existing catheter into the superior or inferior vena cava, freeing the retention cuff from the surrounding tissues using blunt dissection, and removal of the catheter. Disruption of the CRS can be accomplished by advancing a modest diameter (6-8 mm) angioplasty balloon catheter and performing inflations along the previous course of the catheter; see Figure 5. A new catheter is then advanced over the guide wires and through the existing subcutaneous tunnel. When performed using strict sterile technique, there is no increased risk for infection. This strategy has the advantage of preserving the existing venous access site. The less invasive nature of this procedure is responsible for its current widespread application.

Endoluminal brushing of occluded hemodialysis catheters during thrombolysis has been reported with success [69]. This technique targets only the inner lumen of the catheter, not the external CRS.

6.4. Catheter material, coatings and shape

A multitude of tunneled hemodialysis catheters have been marketed over the years with differences in catheter material, tip shape, number of side holes and surface coatings with the hope of reducing complications. While the effects on infection rates and thrombosis of these different catheter types have been studied, rigorous examination of different catheter types on CRS formation is less well understood.

Catheter material has traditionally been variants of either silicone or polyurethane. More recently carbothane has been introduced allowing for greater catheter wall strength and resistance to certain chemicals. In vivo studies of catheter material with regard to thrombogenicity and platelet adhesion have had mixed results showing both no difference between polyurethane and silicone [70] and lower thrombogenicity with polyurethane [71]. Unfortunately, these studies did not evaluate the relationship between thrombogenicity and CRS formation.
A variety of antibiotic and antithrombotic catheter-bound coatings have been developed to prevent infection and thrombosis. As expected, studies have shown that heparin-coated central venous catheters can reduce central venous catheter thrombotic complications [72,73]. A retrospective study published in 2009 evaluated the differences in primary patency between heparin-coated and uncoated hemodialysis catheters. Primary patency at 30 and 90 days demonstrated a slight trend favoring the heparin-coated catheters, but the results did not reach statistical significance (p=0.08) [74].

Variations in catheter tip shape, number of lumen and number of side holes continue to evolve with promises of decreased recirculation, rates of thrombosis and improved flow rates. A
randomized prospective evaluation of three catheter configurations—paired catheters, split tip catheters, and stepped lumen catheters was published in 2001. Despite different design and arrangement of side holes or lumens, all three catheters had similar survival times and flow rates [75]. In 2008, Kakkos et al attributed differences in tip shape to the significant improvement in 90 day primary assisted patency of the Tal Palindrome Ruby (Covidien; Mansfield, MA, USA) catheter compared to the HemoSplit (Bard Access Systems; Salt Lake City, UT, USA) tunneled catheter, 94\% versus 71\%, respectively [76]. This difference persisted at 180 days.

6.5. Future directions

Considerable effort in current interventional cardiovascular research is focused on drug-eluting coatings for stents [77]. These coatings consist of cytostatic or cytotoxic agents that target cell populations involved in stent related restenosis. The characterization of the cellular basis of catheter-related sheath formation may initiate further developments in the area of catheter technologies [78] that could include the development of materials with or without coatings that prevent, retard, or eliminate the sheath.

7. Summary

Catheter-based hemodialysis remains an important option for many chronic kidney disease (CKD) patients. In addition to catheter-related infections, CRS formation is responsible for a significant proportion of catheter dysfunction. It is a dynamic and on-going response of the vein wall to the catheter and the associated thrombus. It involves biologically active cell types and there are many similarities with the process of thrombus organization. There have been numerous methods developed to restore catheter function; thus far, none have provided consistent long term, durable results.

Nomenclature

Chronic kidney disease (CKD), catheter-related sheaths (CRS), percutaneous catheter related sheath stripping (PCRSS)

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