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**Association Between Disruption of Fibrin Sheaths Using
Percutaneous Transluminal Angioplasty Balloons and
Late Onset of Central Venous Stenosis**

A Thesis Submitted to the
Yale University School of Medicine
In Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by
Nina Ni
2011

ASSOCIATION BETWEEN DISRUPTION OF FIBRIN SHEATHS AND LATE ONSET OF CENTRAL VENOUS STENOSIS

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This study compares the rates of central venous stenosis in patients undergoing hemodialysis who underwent disruption of fibrin sheath with percutaneous transluminal angioplasty (PTA) balloons and those who underwent over the wire catheter exchange.

This study is a retrospective review of 209 PTA balloon disruption and 1,304 over the wire catheter exchange procedures. Approval from the Human Investigations Committee was obtained for this study. Up to ten year follow up was performed. A χ^2 test was used to compare the rates of central venous stenosis after balloon disruption versus catheter exchange. A T-test was used to compare time to central venous stenosis development.

Of the 753 patients in the study, 127 patients underwent balloon disruption of fibrin sheath and 626 had catheter exchange. Within the balloon disruption group, 18/127 patients (14.2%) subsequently developed central venous stenosis, compared with 44/626 (7.0%) in the catheter exchange group ($P < 0.01$, χ^2 test). Time to central venous stenosis development was approximately 3 years in both groups and not significantly different

(1,371 and 1,010 days, $P=0.20$). Twenty five point two percent of patients in the balloon disruption group had 4 or more subsequent catheter exchanges versus 12.6% in the catheter exchange group ($P<0.01$, χ^2 test).

There is a possible association between PTA balloon disruption of fibrin sheath and late-onset central venous stenosis. Since venography was not routinely performed in catheter exchange patients, future randomized studies are necessary to confirm these findings.

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Introduction

Hemodialysis catheters

In the U.S., approximately 25% of hemodialysis patients use catheters for hemodialysis, up from 13% over ten years ago.(1, 2) It has been reported that as many as one in five new dialysis patients start their treatment with tunneled cuffed catheters.(3) Dialysis catheters are used either as temporary solutions while patients wait for fistula preparation or kidney transplantation, or as the sole chronic access method. Complications associated with dialysis access are on the rise, as patients diagnosed with end stage renal disease (ESRD) are increasing both in age and in the number and severity of co-morbidities.

Hemodialysis patients currently have high rates of morbidity and mortality, and the vascular access catheters are a contributing factor to these clinical outcomes. The main problems associated with long-term catheterization include thrombosis, vascular stenosis, and infection.(4, 5) Consequently, newer catheter designs often aim to address these issues with innovations over existing products.

Maintaining patients on hemodialysis catheters for the long term is suboptimal from both patient comfort and healthcare cost perspectives. NKF-K/DOQI guidelines recommend that less than 10% of chronic renal failure patients be maintained on dialysis catheters, due to the high rates of complications.(6) In terms of healthcare cost, the U.S. spends \$1-1.5 billion annually on maintaining patients who use hemodialysis catheters.(7) However, only 10% of that is the actual cost of the dialysis catheters themselves. A large

portion of this cost goes toward the hospitalization and procedural costs necessary to manage post-placement complications and catheter exchange. Therefore, careful selection of dialysis catheters and appropriate management of these events can yield much patient and social benefit.

Catheter materials

Short term/ acute catheters

In general, short term central venous catheters for hemodialysis do not have a Dacron retention cuff and are not tunneled.(8) While the majority of long term CVCs are tunneled due to their reduced complication profile, non-tunneled short term catheters are easier to place and remove. These catheters can be rapidly replaced by guide-wire at the bedside and without surgeon or radiographic guidance. Therefore, the catheter shaft must be rigid enough to progress through the subcutaneous tissues. They may also be precurved for jugular placement over the clavicle to reduced patient discomfort and catheter movement-related injury at the exit site.(9)

The current standard short term catheter is a dual lumen catheter, with the venous port 2-3 cm distal to the arterial port to prevent recirculation.(10) Selecting between the two major biomaterials, polyurethane and silicone, reflects a tradeoff between ease of placement and blood flow. The rigid polyurethane catheter can be more easily placed over guidewire without a sheath. The material provides an initial stiffness upon insertion, but then softens when exposed to body temperature.(11) It can also withstand high negative aspiration pressures, permitting adequate hemodialysis with a smaller diameter

catheter. Newer designs utilize silicone to provide a larger lumen for higher blood flow, reaching 400 ml/min or greater as opposed to 250 ml/min with polyurethane catheters.(10) However, due to the flexibility of the material, a peel-away sheath must be employed.

The acute dialysis catheter market in the United States consists of 5 major catheter manufacturers: Covidien, Arrow, Bard, Angio Dynamics, and Medcomp. Covidien MAHURKAR, Arrow, Bard Niagara, and MedComp Duo Flow acute dialysis catheters are made from polyurethane. Other catheters, such as the Angio Dynamics Schon XL and Medcomp Hemocath are made from silicone and include insertion stylets to provide rigidity upon insertion.

Chronic catheters

According to NKF-K/DOQI guidelines, long-term tunneled cuffed catheters should be inserted when anticipated use is three weeks or longer.(6) These long-term catheters are designed to be soft so that endovascular trauma can be minimized. A rigid shaft and tapered tip, which make the acute hemodialysis catheter easy to insert, also renders it unsuitable for long term use. If left for a long time within the superior vena cava or right atrium, the rigid, sharp material could cause significant injury to the tissues.(12)

Chronic hemodialysis catheters are almost always tunneled, with a bonded cuff for anchoring and for preventing bacterial migration. Central venous access has been associated with bacteremia incidences of 2-7 cases per 1,000 catheter days. However, the rate for untunneled catheters range from 3.8-6.5/1,000 catheter-days, and 1.6-5.5 for tunneled cuffed catheters.(13-17) While these retrospective studies differ in definition

and protocol, a meta-analysis of randomized, controlled trials by Randolph et al demonstrated that cuffing and tunneling of catheters reduces the risk for catheter-related bacteremia by 44-77%.(18) Tunneled catheters have also been shown to confer lower infection and hospitalization rates.(19-22)

The chronic dialysis catheter market in the United States consists of the following catheter manufacturers: Covidien, Arrow, Bard, Angio Dynamics, Medcomp, Boston Scientific and Spire. The majority of these chronic catheters are made from polyurethane, which provides an initial stiffness upon insertion, but then softens when exposed to body temperature. Other catheters, such as the Covidien Permcath, Medcomp Hemo-Cath, and Medcomp Hemo-Flow are made of silicone.

Historically, long-term access devices were made from medical grade silicone rubber. It offered a soft, flexible material causing less damage to the intima of the vein on insertion. Its biocompatibility, relatively non-thrombogenic surface, and resistance to chemicals help increase longevity and minimize complications such as thrombosis and infection. The catheters are generally autoclaved or EtO gas sterilized. The softness of the silicone polymer also allows for a larger lumen and placement within the right atrium for maximum blood flows. However, due to its inherent softness, silicone catheters often require thicker walls prevent collapse under low pressures and avoid kinking.(23) Additionally, the necessity of a large diameter peel-away sheath implies a larger cannulation hole in the vein.

Advances in material technology have resulted in the transition from silicone based dialysis catheters to the use of polyurethane. Thermoplastic polyurethanes (or melt-processable polyurethanes) are used extensively in medical devices. They are composed

of long-chain linear polymers without cross-links, which are weakly bonded at room temperature, but become free to slide past one another under sufficient thermal energy—such as provided by the body.(24) Compared with silicone catheters of the same French size, polyurethane catheters can have larger internal diameters without sacrificing rigidity outside the body and flexibility within the body. The increase in lumen diameter results in increased blood flow rate. The catheters are easy to insert, as they soften upon entry into the body. A good catheter must also have sufficient column strength, enabling it to advance into the body with minimal tangling. Like silicone catheters, these products are also biocompatible, non-thrombogenic and EtO gas sterilized. In the case of multi-lumen polyurethanes catheters, thin intra-luminal walls can be constructed, which allow for the maximum number of lumens while maintaining a minimum outer diameter.

Carbothane is a polyurethane/polycarbonate copolymers that affords strength for longevity and softness for flexibility and patient comfort. With slightly greater strength than polyurethane, it can afford to have thinner walls. Unlike polyurethane, copolymers are also resistant to iodine, peroxide, and alcohols. In the future, the majority of chronic catheters are expected to be constructed from copolymer materials.(23)

In vitro and in vivo comparisons between silicone and polyurethane as catheter materials remain inconclusive. Animal models appear to attribute an increased infection risk and thromogenicity to silicone catheters over polyurethane catheters.(25, 26) It might be that silicone catheters have a rougher topography, and are more prone to construction failures because of the more difficult manufacturing process.(27) However, in a study comparing silicone and polyurethane CVCs inserted at the cubital fossa, neither material was found to be superior in thrombogenicity, platelet adhesion, or catheter occlusion

rate.(28) In a study of urethral catheter surface properties, there is even some evidence that silicone-based materials exhibit a greater ease of removal than polyurethane-based materials, due to greater surface lubricity.(29) Ion implantation of silicone rubber has been instrumental in improving silicone's hydrophilicity and lending it resistance to biomaterial deposits. Additionally, polyurethane reacts strongly to alcohol, and the only antibiotic ointment that can safely be used at the exit site is Neosporin. Silicone, on the other hand, is compatible with most ointments.

Although catheter materials are selected to be biocompatible and hemocompatible, complications due to thrombosis and infection are still inevitable. To date, central access for hemodialysis is still inferior to peripheral access via arteriovenous fistula or graft.

Catheter coatings

The use of antithrombogenic and anti-microbial surface technologies on the catheters is one way of reducing the likelihood of complications due to thrombosis or microbial colonization. In acute catheters coated with antibiotics, silver, or heparin the number of infections can be reduced substantially. Heparin-coated catheters, in particular, may confer the additional benefit of cost-effectiveness.(30)

Heparin-coated catheters presents a way to decrease infection rate without the risks of systemic antibiotic exposure or bacterial resistance. Heparin exhibits anticoagulant activity via interaction with the plasma protein antithrombin as well as some electrostatic repulsion of charged platelets. Therefore, it can reduce bacterial trapping within fibrin clots and sheaths.(31) Hydrophobic and electrostatic interactions

also decrease direct bacterial adhesion onto catheter polymer. Heparin immobilized on a plastic surface has been reported to diminish both fibronectin deposition and to decrease bacterial adherence in vitro.(31, 32)

Several studies have demonstrated the safety and efficacy of using heparin-bonded catheters in vivo. In blinded, prospective studies of critically ill children requiring femoral or central venous catheterization, two groups of researchers have found that heparin-bonded catheters are associated with significantly fewer thrombotic complications and a reduced incidence of infection.(33, 34) The major prospective clinical study of heparin-bonded central venous catheters is a 1996 study by Appelgren et al.(31) In vitro, coagulase-negative Staphylococci adhered less to heparinized catheters than to control catheters. The clinical study, while small (32 patients), showed that heparinized catheters are associated with a significant decrease in catheter-associated bacteremia (26% vs. 0%, $p = .047$) and bacterial colonization (31% vs. 74%, $p = .03$).

Covidien offers the Tal Palindrome Emerald hemodialysis catheter, which incorporates a non-eluting heparin coating technology developed by BioInteractions Ltd. Through in vitro and in vivo testing, this coating has been shown to reduce platelet adhesion and thrombus accumulation on the catheter surface. The coating design adopts a multifaceted approach to hemocompatibility, by containing functional groups that have demonstrated performance in hydrophilicity, minimizing platelet adhesion, non-thrombogenicity and anti-thrombogenicity.(35)

Spire Biomedical Inc. offers a heparin coated hemodialysis catheter, marketed as the Decathlon Gold, which includes the Carmeda BioActive Surface (CBAS) coating. The CBAS coating technology has also been shown to reduce platelet adhesion and

thrombus accumulation on the catheter surface through in vitro and in vivo testing. In addressing one of the key problems related to systemic anticoagulation with heparin, the CBAS “end-point” attachment method provides a stable heparin-biomaterial bond that allows for locally-expressed heparin activity at the catheter surface.(36)

The use of other coating materials such as silver and antibiotics has also been promising. While results have been significant for acute use, studies on chronic hemodialysis catheters have yielded inconclusive results. For silver coated catheters, Trerotola et al. showed no statistically significant difference in infection rate between the 47 patients in the treatment group versus the 44 patients in the control group. Two of the silver-coated catheters were also prematurely removed due to silver allergy.(37) However, data from a more recent large-scale prospective study reveals that silver coating can have an anti-microbial benefit: in long-term coated catheters, bacterial colonization was observed on 11% of catheter tips, versus 44% for uncoated catheters.(38) The key difficulty with coating chronic hemodialysis catheters is that the bonded substance can disappear over time, rendering them ineffective over long periods.(39)

Covidien also offers the Tal Palindrome Ruby[®] which incorporates an anti-microbial silver ion sleeve bonded between the hub and the cuff. This sleeve delivers silver ions to the surface of the catheter to reduce microbial colonization on the catheter surface within the tunnel track. In vitro testing with clinical isolates of *Staphylococcus aureus*, Coagulase-negative staphylococcus, *Candida albicans*, and *Escherichia coli* has shown a 99.2%-99.999% (2.1-5.5log₁₀) reduction in microbial colonization.(35)

Covidien is also offering a chronic dialysis catheter that provides both anti-thrombogenic and anti-microbial technologies on one catheter, the Tal Palindrome

Sapphire[®]. The catheter combines the heparin coating technology with an anti-microbial silver ion subcutaneous sleeve.(40)

The Bard Hemosplit[®] and Hemostar[®] catheters include the BioBloc coating, which is an eluting silver sulfadiazine technology intended to reduce bacterial adhesion on the catheter by 99.9% in the catheter tunnel for a period of twenty-one days. The company has performed in vitro tests against *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida albicans*, *Enterococcus faecalis*, and *Escherichia coli*.(41)

Antibiotic-impregnated catheters have also shown significant anti-infective benefit. Antibiotics, most commonly a combination of minocycline and rifampicin, coat both the inner and outer surfaces of the catheter. There have been many clinical trials of coated catheters compared with uncoated controls or head-to-head against other coatings. In a 2008 review of 37 of these randomized controlled trials involving 11,586 patients, Gilbert and Harden conclude that heparin-coated and antibiotic-impregnated central venous catheters lead to significant reductions in catheter related bacteremia, while no strong evidence exists for antiseptic catheters (coated with chlorhexidine and silver sulphadiazine, or silver-impregnated).(42) All relative risk calculations from the studies indicate a strong positive effect of antibiotic coating on the rate of catheter-related bloodstream infection. However, there is also some evidence of antibiotic resistance from in-vitro studies. Additionally, only two major prospective studies involve average catheter use over two weeks, raising the question of antibiotic impregnation longevity.(43, 44)

Recently, Angiotech received 510k clearance on a central venous catheter coated with 5-fluorouracil (5-FU). Since 5-FU is not used routinely in hospitals as an antibiotic, the drug has the unique ability of inhibiting bacterial growth and metabolic functions of most microorganisms while reducing the risk for creating resistant strains. Coating a catheter with a minimal amount of 5-FU renders the surface hostile for microbes, without significant changes in patient tolerability profile.(45) The data from Angiotech's 960 patient clinical trial comparing its 5-FU CVC with a chlorhexidine/silver sulfadiazine (CH-SS) coated CVC shows non-inferiority. However, the 5-FU device appears to be superior in the nature of the colonizations and infections: while the 5-FU coated CVCs were colonized with *S. epidermidis* and other common contaminants, the catheters with CH-SS were also colonized with methicillin-resistant *S. aureus*, *E. coli*, *K. pneumoniae*, *P. mirabilis*, *S. marcescens*, and *A. baumannii*.(46)

Catheter lumen and tip design

Several lumen designs have emerged over the years. The earliest tunneled cuffed catheter, the PermCath by Quinton, was a large, oval shape with two separate lumens. Subsequent improvements have included a round lumen with a central wall, two separate single lumen catheters for differential placement of the inflow and outflow catheter (Tesio, MedComp), and fusion of the two single lumens at a distal point along their length for easier insertion (Ash Catheter, Medcomp).(10)

Two key prospective randomized studies have demonstrated that while double lumen and two single lumen catheters do not lead to appreciable differences in survival or

infection rate, double lumen catheters should be chosen for their ease of use.(27, 47) In a randomized trial of 64 patients, Trerotola et al concluded that the Ash-split catheter and Opti-flow dual lumen catheter had no differences in catheter-related bacteremia and late flow problems.(27) Richard et al compared 38 Ash-split, 39 Opti-flow, and 36 Tesio catheters.(47) The Tesio catheter (two single lumens) required a significantly longer period of time for insertion (mean 42 min versus 29-30 min for the other catheters), leading to more insertion complications. However, mean flow rates and catheter-related infections were not significantly different. These studies demonstrate that in the absence of benefits in post-insertion complications, ease of use may better govern lumen choice.

Commonly used long-term hemodialysis catheters have a staggered tip design, meaning that the outflow tip extends several centimeters (typically a minimum of 2.5 cm) beyond the inflow tip, to prevent recirculation. Another common traditional design is the split tip or dual catheter design. The original split tip catheter is the Ash Split, designed by Dr. Ash and marketed by Medcomp. This catheter has many side holes, thought to facilitate good function. A more recent version of the split tip catheter is the Centros[®] catheter, also designed by Dr. Ash. The rationale behind eliminating the side holes in this model is that the lack of irregular surfaces surrounding the side holes would improve catheter function and survival, and may also reduce infections.

Despite the evolution of tip design, there are few studies on the influence of tip geometry on patient outcomes. The Richard et al study comparing three different tip designs (Tesio dual catheter with side holes, Ash Split Tip with side holes, Opti-flow dual lumen staggered tip with side holes) did not show hemodynamic or catheter survival advantage for any one catheter.(47) The plethora of multiple side hole designs on the

market reflects the belief that backup inflow is necessary in the case of obstruction. However, side holes can also cause thrombosis due the irregularity of their cut surfaces. In a recent comparison of two similar chronic dialysis catheters with and without side holes, Tal et al. demonstrated reduced bacteremia in the non side hole catheters, and attributed the result to reduced thrombus formation at the catheter tip.(48) Mareels et al presented a hemodynamic computer model demonstrating that in a multiple side hole catheter design, the first available hole is primarily employed. The distal holes appeared to comprise a low flow zone, suggesting an increased clotting risk.(49) There is also evidence that side holes can prevent locking solution from reaching the area between the side hole and catheter tip, precipitating clot formation at the tip.(50, 51) Clots may become firmly anchored to the walls around side holes, presenting a difficult to manage situation.

A common drawback of many of the current catheter designs is high levels of recirculation upon lumen reversal, leading to subsequent flow failure. Reversal of the lumens in long-term dialysis catheters is usually performed to correct inadequate inflow, where the inflow through the arterial lumen is inadequate.(8) However, reversal of flow also leads to the undesirable effect of recirculation, whereby dialyzed blood exiting from one lumen directly enters the other lumen, bypassing systemic circulation. Recirculation of blood during dialysis reduces treatment efficiency and can lead to adverse health outcomes.(52, 53)

A more recent catheter designed to address the problem of recirculation is the Tal Palindrome catheter. In this design, the arterial and venous tracts have the same length. While inflow occurs through the side slot and the most proximal portion of the end hole,

outflow occurs as a jet directed away from the catheter tip. This design was found to prevent recirculation in a swine model.(54) Kakkos et al recently demonstrated improved patency and reduced re-interventions with the Palindrome design compared to the split tip design.(55) Catheter patency was significantly higher in the Palindrome Ruby than in the Bard Bioblock. Primary-assisted patency was significantly reduced with the BioBloc (71% and 61% at 90 and 180 days, respectively) compared with the Palindrome Ruby (94% at 90 and 180 days, $P < .0001$).

Catheter-related complications

A catheter's anti-thrombogenic properties are important for longevity, considering that thrombus formation begin as early as 24 hours after insertion.(56) Thrombosis and fibrin sheath can lead to inadequate hemodialysis by disrupting flow. Catheter exchange or fibrin sheath stripping can improve flow, but also introduce further risk for future complications.(57) The continuing development of catheter biomaterials, coatings, and tip designs reflects the need for better durability, as the current median dwelling time is little more than two months. The majority of unplanned catheter removals are due to infection and poor function.(58) Poor function is generally related to flow problems that account for over half of these removals, with 76% of cases exhibiting fibrin sheath formation.(58, 59)

In addition to causing flow problems, catheter thrombosis and fibrin sheath formation have also been implicated in the high rates of catheter-related infection seen in dialysis patients. Infections can be introduced into catheters extraluminally via skin or

intraluminally via the catheter hub. Bacteria can move through the skin insertion site along dermal tunnel and reach the tip of the catheter.(60) Fibrin sheath can exacerbate bacterial colonization by providing a habitable environment. In dialysis patients who are already immunocompromised, bacteria can become trapped in a within the fibronectin coating, rendering them inaccessible to immune cells.(31, 39, 61-63) Bacteria can also adhere to the catheter material itself, forming a protective glyocalix biofilm.(31, 63) The combination of breaking the skin barrier to insert a catheter, exposure to contaminants, and formation of pathogen-trapping fibrin sheaths can cause appreciable bacteremia risk, translating to up to three-fold relative mortality risk.(1, 19) New catheter design and coatings are often emphasized for their effects on reducing fibrin sheath formation and infection rates, which can ultimately lead to decreased morbidity and cost of care.

Vascular stenosis

Central venous stenosis is a significant complication faced by patients who require chronic vascular access. The large-diameter hemodialysis catheters in use today are capable of delivering blood flow rates up to 450 cc/minute, creating hemodynamic stress that may play a significant role in the growing incidence of central venous stenosis.(64, 65) Since detection can be an issue, especially in asymptomatic patients with no indication for venograms, various studies report a wide range of central venous stenosis prevalence rates ranging from 16% to 41% in chronic hemodialysis patients.(64, 66-68) The rate of venous stenosis also depends on catheter dwelling time, history of previous catheter insertion, and insertion site. Various studies show an incidence of 42%

to 50% subclavian stenosis compared with only 0% to 10% internal jugular stenosis.(30, 69) Right-sided internal jugular venous catheters are also less likely to cause stenosis than left-sided catheters, due to the left brachiocephalic vein's more tortuous course and a higher frequency of head motion-related movement with left-sided catheters.(4, 64) In fact, the NKF-K/DOQI guidelines recommend that the subclavian vein should be avoided in chronic renal failure patients who may require permanent vascular access.(6) Nonetheless, subclavian catheters may have a lower risk for infection and are more comfortable for the patient, and are often used for acute renal failure when hemodialysis is temporary.

The pathogenesis of vascular stenosis can be similar to that of thrombosis, precipitated by trauma at sites where the catheter has contact with the vessel wall, especially where the vessel bends or when the cardiac cycle causes motion.(69) Physical damage from turbulence and trauma can result in platelet activation, thrombin generation, and ultimately an inflammatory response. More specific to the central veins, extravascular forces from surrounding structures may also contribute to development of venous stenosis. As the subclavian vein passes through the thoracic outlet, it can be affected by the clavicle, the subclavius and anterior scalene muscles, the first rib, and the subclavian artery. As the left brachiocephalic vein crosses the chest to merge with the right brachiocephalic vein, it must pass the great vessels, sternum, infrahyoid muscles, thymic remnants, and trachea. More proximally, the first rib and sternal border are near the origin of the superior vena cava. These potential extrinsic forces can accelerate the reactive and inflammatory processes within the vessel wall that ultimately lead to stenosis and occlusion.

Patients with central venous stenosis may be asymptomatic, or may present with head and arm edema mimicking cellulitis, pain, dysphagia, and venous varicosities.(65) Obstruction of the subclavian vein is associated with edema and venous hypertension of the ipsilateral arm and breast, while brachiocephalic vein stenosis also affects the face. Bilateral brachiocephalic vein obstruction or superior vena cava obstruction results in superior vena cava syndrome, characterized by edema of both arms, the face and neck, and development of dilated superficial collateral veins over the chest and neck. This condition requires intervention with surgery, angioplasty, or stenting, as it can become life-threatening if soft tissue edema of the neck leads to airway compression. Other complications of central venous stenosis include venous thrombosis, infections, inadequate dialysis, impaired arteriovenous fistula maturation, and decreased fistula and graft patency rate.(70) With a decrease in blood flow caused by the stenosis, subsequent recirculation via the vascular access may result in inadequate dialysis.

In symptomatic cases, percutaneous and surgical solutions offer symptomatic benefit but recurrence is common in the chronic hemodialysis patient with compromised vascular access.(65, 66) Patients with hemodialysis access are much more likely to become symptomatic than nondialysis patients who have central venous stenosis (70% versus 10%). The presence of implantable pacemakers and defibrillators can raise these rates even higher, as they are well-known to cause vessel damage.(65) Percutaneous transluminal angioplasty for central venous stenosis is safe and effective, with 1-year patency rates ranging from 12% to 43%.(71, 72) Endovascular stent deployment is indicated if angioplasty alone leaves more than 50% residual stenosis, or if distal flow remains compromised with subsequent persistence of collateral flow. Primary stenting

could also be performed for select lesions to prevent early restenosis. However, the benefit of stents with angioplasty over angioplasty alone is still debated. Stents also suffer a high rate of restenosis secondary to inflammatory intimal reactions, with approximately 25% patency rate at 1 year.(64) Surgical techniques such as internal jugular to axillary vein transposition, axillary-internal jugular vein bypass grafting, or right atrial bypass grafting can be performed, but these procedures are associated with greater morbidity and are therefore reserved for cases refractory to percutaneous intervention.(4)

Role of fibrin sheaths

Vessel trauma induced by procedures to correct catheter malfunction may also accelerate and exacerbate the development of central venous stenosis. Reasons for catheter malfunction include poor positioning or kinking, and obstructive thrombus or fibrin sheath formation. Fibrin sheath formation is a common cause of late catheter failures: 76% of catheters with poor function exhibit fibrin sheaths, with overall incidence cited at 42-100%.(10, 59) Fibrin sheaths usually originate at the site of catheter insertion or the subcutaneous cuff, migrating overtime down the length of the catheter and resulting in catheter dysfunction or other complications such as thrombosis or infection. Fibrin sheath formation can start as early as 1 day after catheterization and encase the catheter by 5–7 days, and the length of the fibrin sleeve composed of smooth muscles can extend variable lengths, sometimes as far as the superior vena cava. In addition to physical obstruction, fibrin sheaths are also associated with venous

thrombosis and can harbor bacterial colonies that increase the rate of infection, significantly decreasing the longevity of the catheter.

The first-line therapy for these malfunctioning catheters include non-invasive procedures such as positional maneuvers, port reversal, and thrombolytic instillation through the catheter.(73) Continuous infusion of lytic enzymes over 2-4-hours is standard therapy. Another, more economical option is to instill a much smaller amount of tissue plasminogen activator combined with heparin overnight.(73) If these procedures do not improve catheter performance, invasive approaches are indicated. For catheters still refractory, the physician may elect to perform over-the-wire catheter exchange without further imaging. Alternatively, venography can be performed to visualize catheter position and evaluate fibrin or thrombotic obstruction. If a fibrin sheath is visualized, both balloon disruption of the fibrin sheath and catheter exchange procedures are routinely utilized to restore flow.(74-78)

Fibrin sheath disruption and catheter exchange

There two main methods of fibrin sheath disruption. One type of procedure requires a femoral puncture, through which a snare is advanced and looped onto the exterior of the catheter, tightened, and pulled cephalad off the catheter tip to strip off the fibrin sheath. Dual lumen catheters may be stripped independently. An intra-luminal guidewire can facilitate additional stripping passes, and the number of passes can be quite variable from case to case.(79) Alternatively, a more definitive procedure involves balloon disruption of the fibrin sheath followed by catheter exchange. The

malfunctioning catheter is first removed over a stiff guidewire inserted through the lumen. An 8- to 12-mm-diameter angioplasty balloon catheter is then advanced over the guidewire and several inflations with back and forth motions within the vein are performed to disrupt the fibrin sheath along the entire length of the access vein. After confirmation of adequate aspiration and forward flow, a new catheter can then be placed over the guidewire.(59)

Reported outcomes following fibrin sheath stripping vary significantly in the literature, perhaps as a result of its dependency on operator experience as well as differences in underlying patient population. The overall median duration of primary patency after the first snare stripping procedure ranges from 9 to 135 days. Technical success rates are high (90-100%) and complication rates low (0-5%) with both types of fibrin sheath disruption procedures.(74, 76, 77, 79-83) Gray et al found a mean 32 days of additional central dialysis catheter function after snare stripping procedures that did not differ significantly from thrombolytic therapy.(79) A study comparing snare fibrin sheath stripping and balloon disruption of fibrin sheath showed no statistically significant difference in cumulative patency rates or median duration of function—135 days with stripping and 75 days with balloon disruption.(77) However, in a recent randomized study, Oliver et al found a median time to dysfunction of 373 days with angioplasty balloon disruption, though not significantly higher than patients who did not undergo sheath disruption.(83)

Over-the-wire catheter exchange is the other most commonly performed procedure to treat failed hemodialysis catheters with or without fibrin sheaths. It is an alternative to catheter removal and de novo catheter replacement at a different site. A

hydrophilic guidewire is first introduced through the catheter lumen in order to preserve access, and the catheter can be removed following blunt dissection of the tunnel cuff. Finally, a new hemodialysis catheter of the same size is inserted over the guidewire.

Like fibrin sheath stripping, catheter exchange procedures are associated with technical success approaching 100% and low complication rates less than 10%.^(77, 82, 84, 85) Duszak et al demonstrated that catheter exchange provides similar catheter longevity and mean duration of function as de novo catheter placement: 30% and 35% at 12 months, respectively.⁽⁸⁵⁾ Overall median duration of primary patency following catheter exchange ranges from 40 to 85 days, and cumulative patency at 6 months is 30-40%.^(77, 82, 84, 85)

Complications of fibrin sheath disruption and catheter exchange

Previous studies comparing outcomes following fibrin sheath stripping and catheter exchange examine catheter patency rates and short-term complications such as infection, rarely with long term follow up beyond 6 to 12 months.^(74, 75, 77, 83, 86) There are even fewer studies directly comparing disruption of fibrin sheath with percutaneous angioplasty balloon versus catheter exchange, and none have found significant differences in outcome between the two procedures. In a retrospective study, D'Othee et al found an immediate technical success rate of 100% and no complications with both procedures. Cumulative catheter patency rates with balloon disruption and catheter exchange were not significantly different at 6 months (39% and 28%, respectively). Median duration of patency was also similar at 75 days and 60 days,

respectively. Oliver et al's prospective study found much longer, but similar, median durations of patency between the two procedures: 373 for balloon disruption and 97.5 days for catheter exchange ($P=0.22$).

While no complications were reported in either study, both studies have small sample size and lack long-term follow-up. The D'Othee study only includes 33 exchange and 15 balloon disruption procedures followed over 6 months, and the Oliver study includes 12 exchange and 18 balloon disruption procedures followed for a minimum of 6 months. Embolization of the disrupted fibrin sheath is a theoretical immediate complication. Based on the pathogenesis of central venous stenosis, we hypothesize that vessel trauma caused by the fibrin sheath disruption procedure and subsequent inflammatory response can lead to central venous stenosis as a long-term complication with significant morbidity.

The clinical link between the mechanical trauma induced by these procedures and the subsequent development of central venous stenosis is not well-explored. To our knowledge, the current study is the first one designed to evaluate late-onset central venous stenosis development after balloon disruption and over the wire catheter exchange. When central venous hemodialysis catheter dysfunction occurs in our practice, some physicians elect to perform a venogram followed by balloon disruption of fibrin sheath while others elect to do a catheter exchange over the wire. We also have an extensive database of long-term follow-up. Our study compares central venous stenosis and number of subsequent catheters exchange procedures in hemodialysis patients with malfunctioning catheters who undergo balloon disruption of fibrin sheath and those who receive a catheter exchange.

Statement of purpose

To compare the rates of central venous stenosis in patients undergoing hemodialysis who underwent disruption of fibrin sheath with percutaneous transluminal angioplasty balloons and those who underwent over the wire catheter exchange.

Materials and methods

Interventional radiology procedures were performed by experienced radiologists at Yale New Haven Hospital. All data collection, reconciliation, and statistical analyses were performed by the author and approved by Dr. Michael Tal.

Design

This study is a retrospective review of patients who underwent balloon disruption of fibrin sheath with percutaneous transluminal angioplasty balloons and over the wire catheter exchange procedures in the past ten years. All data were obtained from a computerized databases and hospital medical records. Approval from the Human Investigations Committee was obtained for this study. The study includes 209 balloon disruption of fibrin sheath and 1,304 catheter exchange procedures performed at a large university hospital over a ten year period from August 1998 to August 2008.

A database was constructed consisting of all visit information for hemodialysis patients who underwent balloon disruption and catheter exchange procedures in the past ten years. All data were retrieved from the institution's radiology database. Indications for these procedures include catheter malfunction, infection, obstruction, and fibrin sheath formation, but were not consistently available. During exchange for catheter dysfunction, some repositioning often occurs. Available corresponding radiology reports for each patient were used to cross-check results and to identify patients who had subsequent central venous stenosis. Based on radiology report findings, significant CVS

was documented as stenosis of 50% or more. Data were also collected on patient age, sex, date of procedure, site of catheter placement, and diagnosis. Finally, hospital records were reviewed to determine discharge status, including time and cause of death, for patients in the study.

Description of procedures

At our institution, over-the-wire catheter exchange and balloon disruption of fibrin sheath stripping are routinely performed to restore flow to malfunctioning catheters, defined as those with flows less than 300 mL/min. All procedures included in the study were performed by an experienced interventional radiologist in the interventional radiology suite. Each radiologist has a personal preference for either catheter exchange or balloon disruption, choosing to perform one on a regular basis.

Catheter exchange was performed in the standard manner, under local anesthesia over a guidewire. The catheters were bluntly dissected from the tunnel and retracted to the brachiocephalic vein. In some patients, injection of contrast was performed with digital subtraction chest imaging to detect the presence of a fibrin sheath or thrombus. In patients with clinical signs of infection, catheters were removed and the tip was sent for culture and sensitivity. A new catheter was then inserted over a 0.035-inch guide wire and advanced under fluoroscopic guidance. Over the years, various brands of chronic tunneled hemodialysis catheters were used.

For radiologists who prefer to perform balloon disruption of fibrin sheath, the procedure of choice at our institution is balloon angioplasty over guidewire. An 8-12 mm

wide, 4 cm long angioplasty balloon (Bard Inc. Tempe, AZ) was inserted over a guidewire and inflated. Under fluoroscopic guidance, the fibrin sheath was disrupted with back-and-forth motions of the balloon in the region of the proximal right atrium to the confluence of the brachiocephalic vein. The balloon was then removed over a guidewire, and a new catheter was partially inserted. Contrast was then injected for confirmation of sheath disruption, and the catheter was fully advanced under fluoroscopic guidance to the proper position. (Figure 1)

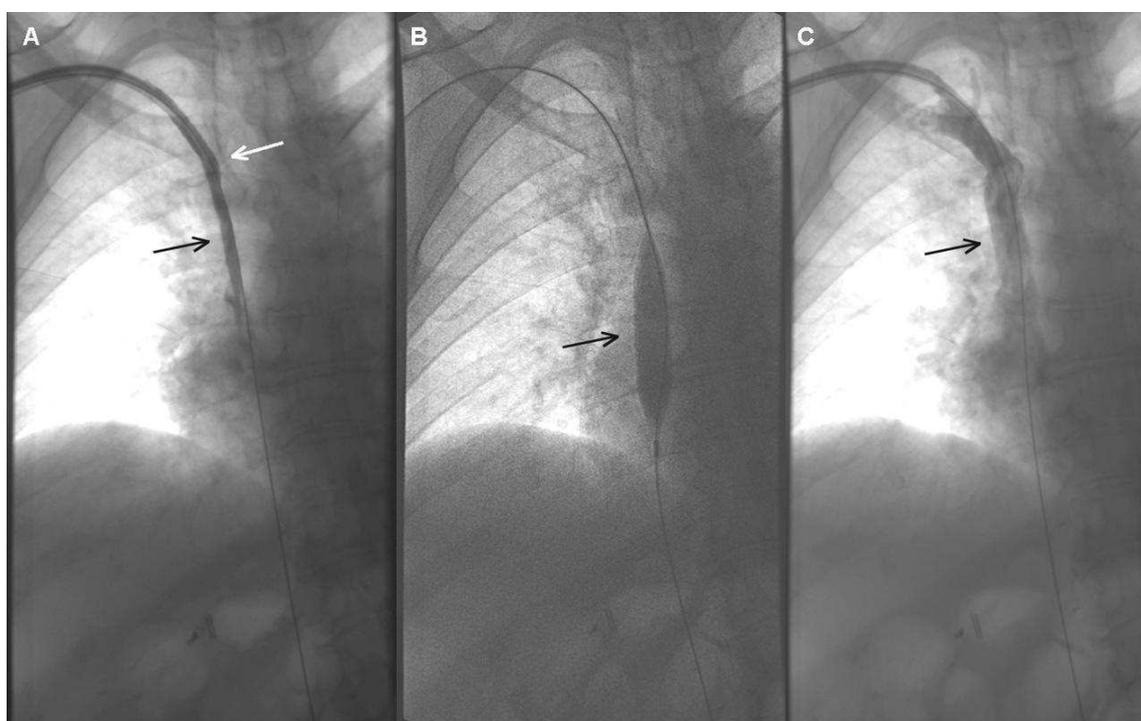


Figure 1: Percutaneous transluminal balloon angioplasty performed over guidewire.

A: After the catheter has been pulled back over guidewire (catheter tip indicated by white arrow), a gentle injection of contrast outlines the fibrin sheath (black arrow). B: A balloon catheter (black arrow) is advanced into the vein. Via back and forth motions under fluoroscopic guidance, the fibrin sheath is disrupted. C: After the procedure,

venogram shows that the vein is patent and the fibrin sheath has disappeared. The black arrow indicates free flow of contrast material.

Outcome measures

A χ^2 test was used to compare the proportions of patients who develop central venous stenosis after balloon disruption versus catheter exchange procedures. Patients who underwent both balloon disruption and catheter exchange procedures were considered in the balloon disruption group. A T-test was used to compare the time to central venous stenosis development, determined from the date of the first balloon disruption or catheter exchange procedure. Finally, a χ^2 test was also used to determine differences in mortality from all causes between the two groups. Differences were considered statistically significant at the $P \leq 0.05$ level.

Results

The study's 209 balloon disruption and 1,304 catheter exchange procedures represent 127 and 626 patients, respectively. There were 79 females and 48 males in the balloon disruption group, and 332 females and 294 males in the catheter exchange group. The average ages are 62.0 ± 1.2 (standard error of the mean) and 60.5 ± 0.5 in the balloon disruption group and catheter exchange group, respectively (Table 1). Mortality by the end of the study was not significantly different between the two groups, with 15.0% in the balloon disruption group and 12.3% in the catheter exchange group ($P=0.41$).

Table 1: Demographic characteristics of the study groups

	Balloon Disruption	Catheter Exchange
Number of Patients	127	626
Female : Male	79 :48	332 : 294
Average Age	62.0 ± 1.2	60.5 ± 0.5

Catheter placement at the time of central venous stenosis diagnosis was also recorded. The majority of catheters were placed in the right IJ in both the balloon disruption and catheter exchange groups (51% and 65%, respectively). There was no statistically significant difference between the two groups. When broken down by the presence of CVS, patients who did and did not exhibit CVS did not differ significantly in the rate of right IJ placement (Table 2).

Table 2: Central venous catheter placement at the time of central venous stenosis

	% R IJ ^A	% L IJ ^B	% L SC ^C	% R SC ^D
Total Balloon Disruption	51%	35%	3%	11%
No CVS ^E	63%	26%	5%	5%
CVS	39%	44%		17%
Total Catheter Exchange	65%	35%		
No CVS	72%	28%		
CVS	42%	58%		
χ^2 tests: R IJ v. L IJ in patients with and without CVS				
Balloon Disruption	$P=0.17$			
Catheter Exchange	$P=0.06$			

^A R IJ: right internal jugular vein. ^B L IJ: left internal jugular vein. ^C L SC: left subclavian vein. ^D R SC: right subclavian vein. ^E CVS: central venous stenosis

Within the balloon disruption group, 18/127 patients (14.2%) exhibited central venous stenosis after their procedure, versus 44/626 (7.0%) in the catheter exchange group ($P<0.01$, χ^2 test). Time to central venous stenosis development after disruption or exchange was not significantly different between the two groups ($1,371 \pm 234$ days for balloon disruption, $1,010 \pm 145$ for catheter exchange, $P=0.20$). The average number of catheter exchanges after a balloon disruption procedure was 2.76 ± 0.36 , compared with 2.02 ± 0.07 after a previous catheter exchange ($P=0.04$). Patients having 4 or more

subsequent exchanges were 25.2% in the balloon disruption group and 12.6% in the catheter exchange group ($P < 0.01$, χ^2 test). (Table 3, Figure 2) The location of CVS was also analyzed. Within the balloon disruption group, superior vena cava stenosis was 31.3% compared with 14.8% in the catheter exchange group, but the difference was not statistically significant. (Table 4)

Table 3: Development of central venous stenosis and number of subsequent catheter exchanges

	Balloon Disruption	Catheter Exchange	P-value
Number of Patients	127	626	
Patients with CVS ^A	18 (14.2%)	44 (7.0%)	<0.01
Days to CVS	1,371 ± 234	1,010 ± 145	0.20
Mortality	19 (15.0%)	77 (12.3%)	0.41
Average # Catheter Exchanges Following Procedure	2.76 ± 0.36	2.02 ± 0.07	0.04
Patients with ≥4 exchanges	32 (25.2%)	79 (12.6%)	<0.01

^A CVS: Central venous stenosis

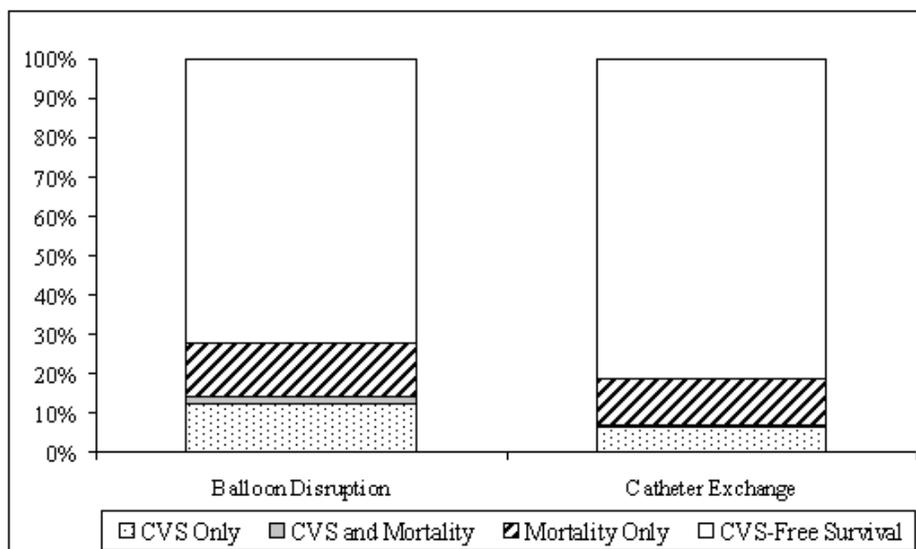


Figure 2: Outcomes following balloon disruption and catheter exchange. CVS: central venous stenosis.

Table 4: Location of central venous stenosis by procedure

	SC ^A	SC-BC ^B	BC ^C	BC-SVC ^D	SVC ^E
Balloon Disruption	0.0%	12.5%	43.8%	12.5%	31.3%
Catheter Exchange	11.1%	14.8%	48.1%	11.1%	14.8%
Combined	7.0%	14.0%	46.5%	11.6%	20.9%

^A SC: subclavian vein; ^B SC-BC: subclavian-brachiocephalic junction; ^C BC: brachiocephalic; ^D BC-SVC: brachiocephalic-superior vena cava junction; ^E SVC: superior vena cava.

Discussion

Central venous stenosis occurring in the subclavian, brachiocephalic veins or superior vena cava is a significant problem in chronic hemodialysis patients. The incidence of central venous stenosis in central venous catheter patients ranges from 3–50%, with internal jugular placement associated with significantly lower rates of 3–10%.(30, 68, 69) Propagation of endothelial injury and neointimal hyperplasia result from prolonged central venous catheterization and arteriovenous shunts.(10, 66, 87) Aside from symptomatic manifestations such as arm or neck swelling, hemodialysis access failure due to decreased vessel patency and increased venous pressure can lead to significant morbidity and mortality.(68, 87, 88) Bilateral central vein stenosis or superior vena cava stenosis can lead to superior vena cava syndrome. Currently, endovascular interventions including angioplasty and stent placement are the mainstay of treatment. Multiple interventions are often required, and surgical bypass is an option. As a last resort, patients will forgo their existing hemodialysis access, and another access point would be established.(64, 70)

Despite the host of complications that can arise from long term use of central venous catheters, their use has risen significantly from 13% of ESRD patients in 1995 to 26% of ESRD patients by 2001.(2) The most common and serious problems associated with long-term catheterization include thrombosis, stenosis, and infection.(4, 5) Fibrin sheath formation can increase the risk of bacteremia by providing a favorable site for microorganism colonization.(4, 31, 63, 89) Based on the 300 ml/min minimum flow requirement of the K/DOQI guidelines, 5 to 13% of patients will require additional

procedures to treat dysfunction.(58, 62, 90-92) For malfunctioning catheters refractory to repositioning, flow reversal, saline flushes, or thrombolytic installation, mechanical methods such as balloon disruption of fibrin sheath and catheter exchange are then employed.(4, 8, 20, 22, 81, 84) When fibrin sheath formation is discovered to be the cause of catheter malfunction, sheath disruption can be performed percutaneously via a gooseneck snare, J-tipped guide wire, pig-tail catheter, or balloon catheter.(8, 73, 75, 76, 78) Alternatively, catheter exchange over guidewire can be performed, though not always accompanied by a search for etiology. While several previous studies have shown that catheter patency rates do not differ significantly between these procedures, we examine the long term outcome of the patient.(74-76, 78)

In studies that have compared clinical outcomes after fibrin sheath disruption and catheter exchange, the focus has been on catheter patency and hemodialysis adequacy. Earlier studies provide a wide range for the mean primary catheter patency after various methods of fibrin sheath disruption, between one and four months.(74-76, 78) There is some evidence that catheters treated by catheter exchange are significantly more likely to remain patent for up to four months than those treated by fibrin sheath disruption.(75) However, in a retrospective study comparing outcomes after over-the-wire catheter exchange, fibrin sheath stripping from a femoral vein approach, and balloon disruption of fibrin sheath, the authors found equivalence in immediate technical success, complication rates, and mean patency rates.(77) Oliver et al. show in a pilot study that median time to repeat catheter exchange and repeat dysfunction were not significantly different between catheter exchange and catheter exchange with balloon disruption of fibrin sheath.(93) They did find that balloon disruption modestly improves blood flow and urea clearance.

In this study, we aim to compare the occurrence of late-onset central venous stenosis after balloon disruption of fibrin sheath and catheter exchange. In our retrospective series, we demonstrate a possible association between central venous stenosis and balloon disruption of fibrin sheath. The number of subsequent catheters placed was also higher following balloon disruption compared with catheter exchange.

Due to the retrospective nature of the study, however, there are underlying differences in general health and vascular status between the two groups that make it difficult to draw definitive conclusions about outcome differences. Data regarding comorbidities that can influence outcomes as well as the symptoms of central venous stenosis were only available from radiology reports and therefore were neither consistent nor reliable. Most cases of CVS were diagnosed during fistulography and documented as stenosis of 50% or more, decided by the performing radiologist at the time. It was also not possible to determine the length of catheter use for the whole ten-year duration of study because data regarding catheter removal was not reliably documented and could not be reliably analyzed due to the retrospective nature of this study. However, mortality is not significantly different between the two groups, suggesting similar baseline health. Another key underlying difference between the two experiment groups is physician decision. Even though most physicians prefer one of the two methods for the majority of their patients, they may also make individualized decisions based on patient presentation.

It must also be emphasized that a major weakness of this study is that there is an unknown proportion of patients in the catheter exchange cohort who may have fibrin sheaths accounting for their catheter dysfunction. Venograms confirming the presence or absence of fibrin sheaths are not routinely performed in the exchange group. Therefore,

not all catheter exchanges necessarily represent incidences of fibrin sheath occurrence. As a result, it is possible that the fibrin sheath itself, and not the balloon disruption procedure, is the main cause of worse outcomes. During the ten year period, there might have been instances of catheter exchange where a venogram was performed with the intent of stripping but no fibrin sheath was found. These severe limitations of this retrospective study can only be overcome with a prospective long term randomized clinical trial comparing over the wire exchange with balloon disruption.

In summary, central venous stenosis remains a significant problem in chronic hemodialysis patients. This retrospective study suggests a possible correlation between balloon angioplasty for disruption of fibrin sheath and late onset of central venous stenosis. Future randomized studies are necessary to confirm these findings.

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