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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]

Central Vein Catheter-Related Thrombosis in Intensive Care Patients*

Incidence, Risks Factors, and Relationship With Catheter-Related Sepsis

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Objective: To evaluate the incidence and risk factors for catheter-related central vein thrombosis in ICU patients.

Design: Observational prospective multicenter study.

Setting: An 8-bed surgical ICU, a 10-bed surgical cardiovascular ICU, and a 10-bed medical-surgical ICU.

Patients: During an 18-month period, 265 internal jugular or subclavian catheters were included. Veins were explored by duplex scanning performed just before or <24 h after catheter removal. Suspected risk factors of catheter-related central vein thrombosis were recorded.

Interventions: None.

Measurements and main results: Fifty-seven catheters were excluded from the analysis. Therefore 208 catheters were analyzed. Mean age of patients was 64 ± 15 years, simplified acute physiologic score was 12 ± 5 , organ system failure score at insertion was 1 ± 1 , and mean duration of catheterization was 9 ± 5 days. A catheter-related internal jugular or subclavian vein thrombosis occurred in 33% of the cases (42% [95% confidence interval (CI), 34 to 49%] and 10% [95% CI, 3 to 18%], respectively). Thrombosis was limited in 8%, large in 22%, and occlusive in 3% of the cases. Internal jugular route (relative risk [RR], 4.13; 95% CI, 1.72 to 9.95), therapeutic heparinization (RR 0.47; 95% CI, 0.23 to 0.99), and age >64 years (RR, 2.44; 95% CI, 2.05 to 3.19) were independently associated with catheter-related thrombosis. Moreover, the risk of catheter-related sepsis was 2.62-fold higher when thrombosis occurred ($p=0.011$).

Conclusions: Catheter-related central vein thrombosis is a frequent complication of central venous catheterization in ICU patients and is closely associated with catheter-related sepsis.

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Key words: catheter-related sepsis; central venous catheter; duplex scanning; internal jugular vein; subclavian vein; vein thrombosis

Abbreviations: CI=confidence interval; CRS=catheter-related sepsis; OSF=organ system failure; SAPS=simplified acute physiology score

Although catheter-related central vein thrombosis is a well-described complication in hemodialysis, cancer, or total parenteral nutrition patients, it has received much less attention than catheter-related sepsis (CRS).¹ Symptomatic catheter-related central vein thrombosis is infrequent, but the incidence of

asymptomatic catheter-related central vein thrombosis diagnosed by venographic studies can be as high as 66%,² with a 59% incidence rate of pulmonary embolism.³ In these patients, the main risk factors are catheter thrombogenicity,⁴ CRS,⁵ lack of anticoagulation,⁶⁻⁸ absence of IV lipid emulsion use,⁹ and cancer.¹⁰

Since, to our knowledge, catheter-related central vein thrombosis has not yet been studied in a large series of ICU patients, we conducted an observational prospective multicenter study concerning its incidence and risk factors, in particular the relationship between catheter-related central vein thrombosis and CRS.

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MATERIALS AND METHODS

Setting

This prospective study was performed in three ICUs: the 8-bed surgical ICU of the Clinique de la Defense (Nanterre, France), the 10-bed surgical cardiovascular ICU of the Hôpital Saint Joseph, and the 10-bed medical-surgical ICU of the "Hôpital Saint-Joseph" (Paris, France).

Patients and Catheters

The protocol was approved by the ethics committee of Hôpital Cochin (Paris, France). Consecutive patients at least 18 years of age, expected to need a central venous access catheter for at least 48 h, were included. Catheters were inserted via the internal jugular or subclavian vein according to the physician's judgment. Polyurethane catheters, single lumen (6F 14-gauge channel), double lumen (7F, 16-16 gauge channels) or triple lumen (7F, 16-18-18 gauge channels) were used (Plastimed; St Leu la Forêt, France).

Exclusion criteria were previous catheterization of the vein and/or catheter introduced by guide-wire exchange and history of deep venous thrombosis and local trauma at the insertion site.

Under strict aseptic conditions, catheters were inserted at bedside using the Seldinger technique. Physicians were required to wear cap, mask, and sterile gloves and gown. The insertion site was prepared with povidone iodine and draped with sterile towels. Catheters were inserted percutaneously and then covered with sterile occlusive adhesive transparent dressings (Opsite IV3000; Smith and Nephew Med Ltd; London, UK). Chest radiographs were obtained after catheter placement to ensure proper catheter position in the right atrium and to diagnose mechanical complications. IV tubing and transparent dressings were changed immediately in case of dressing violation or routinely every 72 h. Catheter dressings were inspected twice a day by trained nurses for the appearance of local signs of infection and appearance of thoracic collateral circulation. Any use of the catheters except through-the-line blood samples was allowed, including total parenteral nutrition, blood products administration, medication, and central venous pressure monitoring.

Risks Factors for Catheter-Related Thrombosis

Risk factors for catheter-related central vein thrombosis identified or suspected by previous studies⁴⁻⁹ were prospectively evaluated: age, gender, organ system failure (OSF) score,¹¹ simplified acute physiology score (SAPS) at insertion,¹² experience of the physician (senior vs resident), number of catheter lumens, side of venous puncture, duration of insertion procedure, occurrence of multiple vein punctures, occurrence of arterial puncture, internal jugular or subclavian route, platelet count at insertion, presence of shock or cancer, use of lipid emulsion, presence or absence of therapeutic heparinization of the patient, suspicion of CRS at removal, catheter duration, occurrence of CRS, and outcome at 30 days.

Diagnosis of CRS

Catheters were removed and cultured according to the pre-established rules in the event of signs of CRS, uselessness, malfunction, discharge from the ICU, or death. Schematically, catheter infection was suspected and the catheter was immediately removed and culture specimen was obtained in case of the following: (1) purulence of the catheter insertion site; (2) occur-

rence of temperature $\geq 38.3^{\circ}\text{C}$ or hypothermia $\leq 36.5^{\circ}\text{C}$ with associated shock; (3) occurrence of temperature $\geq 38.3^{\circ}\text{C}$ or hypothermia $\leq 36.5^{\circ}\text{C}$ with erythema or tenderness at the insertion site (or of the subcutaneous tunnel) of the catheter and no other cause of sepsis; or (4) occurrence of temperature $\geq 38.3^{\circ}\text{C}$ or hypothermia $\leq 36.5^{\circ}\text{C}$ with positive blood cultures. Decision to remove catheters was made by the medical staff without input from the investigators. Catheter-tip specimens were cultured using a simplified quantitative broth dilution culture technique previously reported to have a 97.5% sensitivity and an 80% specificity for the diagnosis of CRS when $\geq 10^3$ cfu/mL.¹³

Broth cultures were subcultured onto aerobic and anaerobic agar plates, all organisms recovered from any culture were identified, and antibiotic susceptibilities were determined by prescribed methods. Peripheral blood cultures were obtained in the event of fever (temperature $\geq 38.3^{\circ}\text{C}$), hypothermia (temperature $\leq 36.5^{\circ}\text{C}$), local signs of catheter infections, or other indications (chills or sudden shock), and they were processed by the clinical microbiology laboratory according to standard methods. In case of suspected CRS, at least two blood cultures were performed within 24 h.

As previously published,¹⁴ the definitions of systemic CRS were as follows: systemic CRS includes CRS without septicemia and catheter-related septicemia; CRS without septicemia was defined as temperature $\geq 38.5^{\circ}\text{C}$ or hypothermia $\leq 36.5^{\circ}\text{C}$ and catheter tip culture $\geq 10^3$ cfu/mL and (1) pus at the insertion site (or in the subcutaneous tunnel) or (2) resolution of clinical sepsis after catheter removal and no other infectious site. Catheter-related septicemia was defined as one or more positive blood cultures sampled immediately before or for the 48 h of catheter removal (in case of coagulase-negative *Staphylococcus* septicemia, two positive blood cultures were mandatory); plus, either (1) quantitative tip culture $\geq 10^3$ cfu/mL with isolation of the same organism from the catheter or (2) in case of purulence at the insertion site (or in the subcutaneous tunnel), isolation of the same microorganism from the catheter and the bloodstream. Significant catheter colonization was defined by a quantitative tip culture $\geq 10^3$ cfu/mL.¹³

Diagnosis of Catheter-Related Thrombosis

Diagnosis of vein thrombosis was established by color Doppler ultrasound examination performed routinely, just before, or < 24 h after catheter removal. Internal jugular and subclavian veins were classified as (1) without thrombosis or (2) with limited (2 to 4 mm), large (≥ 4 mm), or occlusive thrombosis.

The same team of specialized vascular radiologists performed the examination in the three ICUs, using a 7.5-MHz ultrasonographic real-time imager and a 4.5-MHz probe for duplex spectral-analysis (Ultramark 9; Hewlett-Packard; Andover, Mass). By using infraclavicular and supraclavicular approaches, longitudinal and transversal views were obtained from the subclavian vein. The internal jugular vein was also imaged in both axes along its entire length from the angle of the mandible to the supraclavicular fossa. In the area of the supraclavicular fossa, a coronal image of the junction of the internal jugular and subclavian vein as they unite to form the innominate vein was recorded routinely. The superior vena cava was not demonstrated in any patient due to the lack of a suitable acoustic window.

The diagnosis of catheter-related central vein thrombosis was based on the visualization of an intravascular thrombus, incompressibility of the vein by probe pressure, absence of spontaneous flow by Doppler, and absence of phasicity of the flow with respiration.^{15,16} The diagnosis required direct visualization of thrombus and one or more of the other signs. In case of thrombosis, investigators had to question themselves about the diagnosis of pulmonary emboli using clinical findings, ECG,

Chest radiographs, and blood gas values. In case of suspicion of pulmonary emboli, pulmonary angiogram or lung scanning had to be performed. All reported forms, including all relevant data, were reviewed by two physicians (J.F.T., J.C.F.) blindly for color Doppler ultrasound results.

Statistical Analysis

The main end point was the time to occurrence of catheter-related thrombosis. Time failure data were computed from catheter insertion, estimated by the Kaplan-Meier method. Potential risk factors for thrombosis were studied using log-rank test. Variables found to be associated with the time to occurrence of thrombosis were then entered into a multivariate Cox model.

Finally, the relationship between thrombosis and significant catheter colonization or CRS was performed using Fisher's Exact Test and adjusted for local signs of infection and cause of catheter removal using logistic regression.

Groups were compared by using two-sided tests, with *p* values of ≤ 0.05 denoting statistical significance.

RESULTS

Population

Two hundred sixty-five consecutive patients were included in the study. Fifty-seven (21%) were excluded from analysis: 25 because duplex scanning was not available just before or at least 24 h after catheter withdrawal (when catheters were removed on Saturday, 25 cases; death before catheter removal and duplex scanning, 16 cases; catheters not cultured, 10 cases; catheter duration was <48 hours, 3 cases; nonvisualization of a segment of the subclavian vein with duplex scanning related to acoustic shadowing of the clavicle in patients with subclavian catheters, 3 cases).

None of the 10 patients without catheter culture had sepsis. Postmortem examination was performed in 6 of the 16 patients who died before duplex scanning and did not find any case of pulmonary embolism. The incidence of catheter-related colonization and CRS in patients excluded from the analysis and for which the information was available was 10 of 47 and 4 of 47, respectively.

Therefore, analysis included 208 patients. Patients were aged 64.6 ± 15 years, with a mean OSF score at 1 ± 1 and a mean SAPS at 12 ± 5 . Diagnoses on ICU admission were mainly infectious diseases (35%), postoperative care (34%), cardiovascular failure (18%), respiratory failure (7%), and neurologic failure (6%). The 30-day mortality rate of patients included in the analysis was 13%.

The catheters were removed after 9.35 ± 5.4 days. The reasons for catheter removal were uselessness ($n=108$), suspicion of infection ($n=86$), discharge ($n=9$), death ($n=1$), and malfunction ($n=4$).

Incidence of Catheter-Related Central Vein Thrombosis

Catheter-related internal jugular or subclavian thrombosis was diagnosed in 69 of 208 of the patients (33%). Internal jugular and subclavian catheter-related central vein thrombosis occurred in 41.7% (95% confidence interval [CI], 34 to 49%) and 10.5% (95% CI, 3 to 18%) of the patients, respectively. Thrombosis was considered as limited (2 to 4 mm) in 18 patients (8%), large (≥ 4 mm) in 46 patients (22%), and occlusive in 7 patients (3%). Despite the prospective clinical follow-up, none of the 208 patients developed symptoms consistent with central vein thrombosis. Since follow-up duplex scanning was not in the design of the study, only six patients with large or occlusive thrombosis had a second duplex scanning 2 to 5 days after catheter removal. In two patients, the thrombus had completely disappeared. Two patients with occlusive thrombosis underwent pulmonary angiogram because of suspicion of pulmonary emboli. Results of both examinations were normal.

Risk Factors for Catheter-Related Central Vein Thrombosis

Catheter-related central vein thrombosis was not associated with gender, SAPS at insertion, experience of physician, number of lumens, side of venous puncture, duration of insertion, occurrence of multiple vein punctures or arterial puncture, platelet count at insertion, presence of shock or cancer, or outcome at 30 days. Using univariate analysis, age ≥ 65 years, the internal jugular route, OSF score ≥ 1 at insertion, the absence of therapeutic heparinization, and the absence of use of lipid emulsion were risk factors for catheter-related thrombosis. Three factors were independently associated with catheter-related central vein thrombosis: age ≥ 65 years, the internal jugular route, and the absence of therapeutic heparinization (Table 1).

Relationship Between Catheter-Related Thrombosis and CRS

Forty-nine of the 208 catheters (23.5%) grew $>1,000$ cfu/mL and 23 (11.1%) were involved in CRS, including 13 (6.25%) with catheter-related septicemia. The presence of CRS or significant catheter colonization was more frequent in patients whose catheter-related central vein thrombosis was diagnosed (Table 2).

Thrombosis was equally distributed in patients with or without local signs of infection (no local signs, 54/139 vs local signs, 31/69; $p=0.35$). Catheter-related thrombosis remained associated with catheter-

Table 1—Risk Factors for Catheter-Related Thrombosis

	No. of Cases/ No. of Events	Univariate (p Value Log Rank Test)	Multivariate*	
			RR (95% CI)	p Value
Baseline characteristics				
Age, yr				
<65	81/20			
≥65	127/49	0.0001	2.44 (2.05-3.19)	0.001
Gender				
Male	143/50			
Female	65/19	0.19		
SAPS				
<12	94/31			
≥12	114/38	0.21		
Cancer				
Yes	17/6			
No	191/63	0.37		
Surgical patients				
Yes	131/40			
No	76/29	0.17		
At the time of catheter insertion				
OSF				
<1	77/17			
≥1	131/52	0.009	1.07 (0.59-1.96)	0.5
Shock				
Yes	62/20			
No	146/49	0.06		
Platelet, 10 ⁹ /L				
<250	104/32			
≥250	104/37	0.14		
Side of venous puncture				
Left	93/27			
Right	115/42	0.33		
Jugular access				
Yes	151/63			
No	57/6	0.0001	4.13 (1.72-9.95)	0.005
Duration of insertion, min				
<20	114/35			
≥20	94/34	0.42		
Complication during insertion†				
Yes	46/18			
No	162/51	0.14		
Experience of the operator				
Resident	93/31			
Senior physician	115/38	0.46		
Gauge				
6F	70/20	0.28		
7F	138/48			
No. of lumens				
1	69/19			
2	122/46	0.91		
3	18/4			
During catheter maintenance				
Therapeutic anticoagulation				
Yes	43/9			
No	165/60	0.027	0.47 (0.23-0.99)	0.04
Lipid infusion				
Yes	128/43			
No	80/26	0.03	0.65 (0.39-1.08)	0.1
Corticosteroids				
Yes	23/8			
No	195/58	0.13		

*RR=relative risk.

†Arterial puncture or multiple venous punctures.

Table 2—Relationship Between Thrombosis and Infection

Event, No. (%)	Thrombosis, (n=69)	No Thrombosis (n=139)	Likelihood Ratio* (p Value)
Significant catheter colonization	22 (32)	27 (19.4)	1.64 (0.046)
CRS	13 (19)	10 (7)	2.62 (0.011)
Catheter-related septicemia	8 (11.6)	5 (3.6)	3.22 (0.025)

*Indicates the relative risk of CRS, catheter related septicemia, or significant catheter colonization when thrombosis is diagnosed.

ter-related infection even after adjustment with the presence of local signs of infection (odds ratio, 2.97; 95% CI, 1.17 to 7.53; $p=0.02$, logistic regression).

Pathogens responsible for CRS were *Staphylococcus aureus* (n=4), coagulase-negative *Staphylococcus* (n=4), *Klebsiella* species (n=4), *Acinetobacter* species (n=4), *Serratia* species (n=2), *Pseudomonas* species (n=2), *Enterobacter* species (n=2), and other strains (n=5). Incidence of thrombosis was not more frequent in catheters that grew *S aureus* as compared with other strains.

DISCUSSION

Although central venous catheterization has been a routine technique for many years, to our knowledge, this is the first large prospective multicenter study on the incidence and risk factors of catheter-related central vein thrombosis in ICU patients.

We found that asymptomatic catheter-related thrombosis was frequent in the ICU and was associated with an older age, a jugular access, and the absence of therapeutic anticoagulation. However, the clinical relevance of catheter thrombosis must be questioned since no patients were symptomatic. This study confirmed the relationship between CRS and catheter-related thrombosis.

Fifty-seven patients (21%) were excluded from the analysis. This might have changed the estimated risk of catheter-related thrombosis. However, the incidence of CRS was not different in these patients as compared with that of the patients included in the analysis, and the exclusion criteria were mainly due to unavailability of duplex scanning or technical issues.

Major complications of catheter-related central vein thrombosis are suppurative thrombophlebitis, propagation in superior vena cava or intracranial sinuses or veins, and pulmonary embolism.¹⁷ Subclavian and internal jugular thrombosis account for 1 to 4% of all deep vein thromboses. Catheterization accounts for one third of the cases of upper-limb vein thrombosis.¹⁸ Incidence of catheter-related central vein thrombosis varies with catheter composition, indication of catheterization (total parenteral

nutrition, hemodialysis, hemodynamic monitoring, cancer or ICU patient), fluids infused (chemotherapy, lipids, or heparin), and diagnostic method for thrombosis.

Clinical incidence of catheter-related central vein thrombosis is as low as 0 to 4%:¹⁹ numerous venous collaterals of the upper extremity minimize the hemodynamic effects of thrombosis.⁹ Nevertheless, catheter-related thrombosis was not associated with clinical symptoms. Literature reviews of autopsy or venographic diagnoses found a fibrin sleeve formation in 80%, and a mural or occlusive thrombus in 8 to 54% of patients.^{1,19-21} Chastre et al² found a 66% incidence of complete asymptomatic thrombosis of internal jugular vein after Swan-Ganz catheterization.

The incidence of pulmonary embolism due to catheter-related central vein thrombosis in ICU patients is unknown. In an autopsy study, catheter-related central vein thrombosis occurred in 50% of patients with the Swan-Ganz catheter, with a 59% incidence of distal pulmonary embolism and 16% of proximal pulmonary embolism.³ In other series, the reported incidence of pulmonary embolism ranged between 11% and 36%^{2,18,22,23} of the patients with catheter-related central vein thrombosis. However, the presence or absence of pulmonary emboli was not different for patients with or without mural thrombi.²⁴ In a recent series of pediatric patients with total parenteral nutrition,²⁵ the survival rate free from fatal pulmonary thromboembolic events was as low as 74% at 5-year follow-up. The analysis of pulmonary embolism occurrence was not a goal of the present study and no diagnosis of pulmonary embolism due to catheter-related central vein thrombosis was made. Nevertheless, the diagnosis of pulmonary embolism in the ICU patient with rapid hemodynamic variations or pulmonary gas exchange is difficult and the true incidence could have been largely underestimated.²⁶ In this series, two patients had a large catheter-related central vein thrombosis that disappeared <5 days after catheter removal without experiencing any sign of pulmonary embolism.

Internal jugular thrombosis was diagnosed much

more frequently than subclavian thrombosis (relative risk, 4.13). This result is contradictory to other reports in which subclavian thrombosis occurred more²⁴ or as frequently²¹ as internal jugular vein thrombosis. The role of the impaction of the tip of the catheter or its introducer sheath when negotiating the angle of the innominate-caval junction that may have focally eroded the endothelium and predisposed to mural thrombi²⁴ has been advocated in previous studies.

The use of Seldinger technique with J guide, and of new less rigid polyurethane catheters, might lead to a dramatic decrease in the risk of endothelial erosion. The risk of thrombosis is increased when a small lumen vein is chosen.²¹ This might explain partly why the thrombosis occurred more frequently while using the jugular route.

The use of duplex scanning and the restrictive definition of catheter-related central vein thrombosis used in this study could have underestimated the real incidence of subclavian catheter-related central vein thrombosis. However, color ultrasound has made, in experienced hands, considerable progress in the accuracy for diagnosis of deep upper and lower vein thrombosis with a sensitivity as high as 89 to 96% and a specificity ranging between 94% and 100%.^{15,16,27} Acoustic shadowing of the clavicle can result in nonvisualization of a short segment of the subclavian vein with duplex scanning.²⁸ Because this occurred in three patients with subclavian catheters, they were excluded from the analysis. Moreover, even with exclusion of subclavian catheters, the relationship among age, absence of therapeutic anticoagulation, and CRS remained significant.

CRS was closely related to catheter-related central vein thrombosis in ICU patients as previously suspected by other authors in other settings.^{4,5,9,10} The incidence of CRS in patients with catheter-related central vein thrombosis was 18.8% (13/69), compared with 7.2% (10/139) in patients without catheter-related central vein thrombosis: the presence of catheter-related central vein thrombosis increased by 2.6-fold the risk of CRS. Therefore, observation of catheter-related central vein thrombosis in patients suspected of having CRS might argue for catheter removal.

It is not known whether catheter-related central vein thrombosis favors CRS or if CRS promotes catheter-related central vein thrombosis. It has been speculated that the fibrin sheath surrounding the catheter develops within 24 h and increases bacterial attachment and replication. Stillman et al⁴ have reported a correlation between catheter thrombogenicity and vulnerability to microbial colonization, probably resulting from ligands in the thrombus that promoted microbial adherence.

Catheter-related central vein thrombosis is less frequent in patients with prolonged prothrombin or activated partial thromboplastin times, or in the case of heparin-bonding, heparin addition to IV fluids, and oral anticoagulant therapy.^{1,3,6-8,29} The potential role of heparin administration or heparin bonding in reducing the incidence of CRS is controversial, but IV heparin seems to reduce the incidence of catheter-associated sepsis when parenteral nutrition is used.³⁰ The significant relationship between the absence of therapeutic heparinization and catheter-related central vein thrombosis, and between CRS and catheter-related central vein thrombosis is an argument for the protective effect of heparin against the occurrence of CRS. Therefore, it would be interesting to repeat the study using heparin-bonded catheters.


This study confirms the close relationship between CRS and catheter-related central vein thrombosis. It also encourages the development of less thrombogenic material and the implementation of further randomized study on the role of anticoagulants or fibrinolytics in CRS in ICU patients. This study was not designed to evaluate the clinical implications of catheter-related central vein thrombosis. The focus was to study its incidence and its risk factors. However, the consequences of catheter-related central vein thrombosis, mainly chronic vein thrombosis and pulmonary embolism, should be explored further.

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Central Vein Catheter-Related Thrombosis in Intensive Care Patients: Incidence, Risks Factors, and Relationship With Catheter-Related Sepsis

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