

## Review Articles/Brief Reviews

# A critical review of thromboembolic complications associated with central venous catheters

*[Une synthèse critique des complications thromboemboliques associées aux cathéters veineux centraux]*

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**Purpose:** Central venous catheters (CVC) are commonly used in critical care. While thrombosis is a well-recognized and frequent complication associated with their use, CVC-related thromboembolic complications, including pulmonary embolism (PE) and right heart thromboembolism (RHTE), occur less frequently and often evade diagnosis. Little information exists to guide clinicians in the diagnosis and management of CVC-related thromboembolic complications.

**Source:** We critically review and synthesize the literature highlighting the incidence of CVC-related thrombosis. We highlight the risk for developing thromboembolic complications and provide approaches to diagnosing and managing RHTE.

**Principle findings:** The incidence of CVC-related thrombosis varies depending on patient, site, instrument, and infusate-related factors. Central venous catheters-related thrombosis represents an important source of morbidity and mortality for affected patients. Pulmonary embolism occurs in approximately 15% of patients with CVC-related upper extremity deep venous thrombosis (UEDVT). More frequent use of transesophageal echocardiography, in patients with suspected and confirmed PE, has resulted in increased detection of RHTE. While it is recognized that the occurrence of RHTE, in association with PE, increases mortality, the optimal strategy for their management has not been established in a clinical trial.

**Conclusion:** Central venous catheter-related thrombosis occurs frequently and represents an important source of morbidity and mortality for affected patients. Our review supports that

surgery and thrombolysis have both been demonstrated to enhance survival in patients with RHTE and PE. However, important patient, clot, and institutional considerations mandate that treatment for patients with RHTE and PE be individualized.

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**Objectif :** Les cathéters veineux centraux (CVC) sont couramment utilisés dans les soins aux malades en phase critique. Bien que la thrombose soit une complication fréquente et bien reconnue associée à leur utilisation, les complications thromboemboliques associées aux CVC, notamment l'embolie pulmonaire et la thromboembolie du cœur droit, surviennent moins fréquemment et échappent au diagnostic. Peu d'informations existent pour guider le clinicien dans le diagnostic et la prise en charge des complications thromboemboliques associées à l'utilisation de CVC.

**Source :** Nous avons revu et résumé de façon critique la littérature soulignant l'incidence de thrombose associée aux CVC. Nous mettons en évidence les risques qui favorisent l'apparition de complications thromboemboliques et proposons des approches permettant le diagnostic et la prise en charge de la thromboembolie du cœur droit.

**Constatations principales :** L'incidence de thromboses associées aux CVC varie selon des facteurs liés au patient, au site, à l'instrument et à la solution intraveineuse choisie. La thrombose

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associée aux cathéters veineux centraux constitue une source importante de morbidité et de mortalité chez les patients affectés. L'embolie pulmonaire survient chez environ 15 % des patients souffrant de thrombose veineuse profonde des membres supérieurs associée aux CVC. Un recours plus fréquent à l'échocardiographie transœsophagienne dans la prise en charge des patients présentant une embolie pulmonaire suspectée ou confirmée a permis de détecter plus souvent une thromboembolie du cœur droit. Bien que nous sachions que la survenue de thromboembolie du cœur droit, lorsque associée à une embolie pulmonaire, augmente la mortalité, aucune étude clinique n'a encore déterminé de stratégie optimale pour sa prise en charge.

**Conclusion :** La thrombose associée à l'utilisation de cathéters veineux centraux survient fréquemment et constitue une source importante de morbidité et de mortalité chez les patients touchés. Notre synthèse appuie le fait qu'il a été démontré que la chirurgie et la thrombolyse améliorent la survie des patients souffrant de thromboembolie du cœur droit et d'embolie pulmonaire. Cependant, des considérations importantes concernant le patient, le caillot et l'institution en cause nécessitent que le traitement des patients souffrant de ces affections soit personnalisé.

CENTRAL vein catheters (CVCs) are an essential component of critical care. Central vein catheters enable invasive monitoring, facilitate atrial pacing and renal replacement therapy, and permit delivery of parenteral alimentation and medications. Notwithstanding, CVCs are associated with serious complications, including infection and thrombosis. We searched Ovid MEDLINE to review, to critically appraise, and to synthesize the peer-reviewed literature highlighting the incidence of CVC-related thrombosis and development of thromboembolic complications, including pulmonary embolism (PE) and right heart thromboembolism (RHTE). More frequent screening of the upper extremities during PE investigation has demonstrated that upper extremity deep vein thrombosis (UEDVT) and CVC-related thromboses are associated with an appreciable risk of PE and death. Increased utilization of transesophageal echocardiography (TEE) in patients with suspected and confirmed PE has facilitated increased detection of RHTE. RHTE includes nonmobile and mobilized deep vein thromboses (DVT) located within the right atrium (RA) or ventricle.<sup>1</sup> While it is recognized that the occurrence of RHTE, in association with PE, increases mortality, the optimal strategy for their management remains uncertain. In this review, we summarize the best available evidence addressing CVC-related thrombosis and the

risk for RHTE formation and PE. We provide an approach to establishing these difficult diagnoses and review available treatment options for managing CVC-related right atrial thrombi (RAT), including surgery, systemic thrombolysis, catheter-directed thrombolysis, and other novel techniques.

### Central vein catheter-related thrombosis

Precise estimates of the incidence of CVC-related thrombosis (thrombi associated with catheters dwelling in the central circulation) are difficult to ascertain. A large population-based, case-control study supports that the risk for thrombosis in patients with a CVC or transvenous pacemaker is increased approximately sixfold.<sup>2</sup> Estimates from case series and observational studies have noted incidence rates ranging from 35 to 67% of long-term catheterizations in critically ill patients.<sup>3,4</sup> The variability in estimates from the literature results from a variety of conditions; for example, use of variable, and often overlapping, definitions for UEDVT and CVC-related thrombi; inclusion of heterogeneous patient populations with symptomatic and asymptomatic presentations; different catheters and insertion sites; diverse diagnostic strategies; sleeve and mural thrombi; and incident and prevalent cases. Patient-related risk factors (including obesity, advanced age, male gender, heparin use, thrombophilic states), catheter-related factors (composition and dimensions), and intensive care-related factors (the requirement for invasive ventilation, sedation and paralysis, and recent trauma or surgery) may contribute to the risk of CVC thrombosis<sup>5,6</sup> (see Table). Over the past decade, technology has evolved from the routine use of materials such as latex, polyethylene, and polyvinyl, to catheters made of silicone, silastic, or polyurethane (with optional heparin bonding or antibiotic coating) to decrease catheter thrombogenicity.

The importance of instrumentation site on the incidence of CVC-related thrombosis has received considerable attention. Estimates of femoral CVC-related thrombosis of 23.3% and 25% have been reported in small randomized controlled trials (RCTs) using venographic and ultrasound confirmation, respectively.<sup>7,8</sup> One study found that triple lumen catheters were frequently placed in the femoral site, and that femoral DVT occurred despite prophylaxis with subcutaneous heparin and/or compression stockings.<sup>8</sup> A large recent RCT, involving 289 critically-ill patients assessed by ultrasound, supported that femoral catheterization is associated with a greater risk of infectious [hazard ratio 4.8 (95% Confidence interval (CI) 2.0 - 11.9)] and thrombotic [odds ratio (OR) 14.4 (95% CI 3.3 - 62.6)] complications compared to subclavian

TABLE Risk factors for deep venous, catheter-related and intracardiac thrombosis

<i>Patient-related</i>	<i>Instrument-related</i>	<i>Infusate-related</i>	<i>Site-related</i>
§ Hypercoagulable states	* Non heparin bonded catheters	* Amphotericin B	* Femoral or § IJ insertion site
*§ Thrombophilic states	* Polyvinyl or polyurethane catheters	* TPN	§ SVC site of insertion
* Age > 64 yr	* More than one CVC simultaneously		§ Concurrent infection
*§ Malignancy	* Temporary venous pacemaker		* Canulation > six days
* Dehydration	* Traumatic insertion		
* Impaired tissue perfusion	* PICC catheter size		
† Chronic hemodialysis	§ Distal catheter position		
* Absent prophylaxis/treatment			

\*Factors associated with central venous catheter thrombosis; §Factors associated with intracardiac thrombus development. CVC = central venous catheterisation; IJ = internal jugular; SVC=subclavian venous catheter; PICC=peripherally inserted central catheter; TPN = total parenteral nutrition.

catheterization with 21.6% of patients, with a femoral catheter, experiencing catheter-related thrombosis.<sup>9</sup> These estimates are supported by a prospective observational study of 140 critically-ill patients, 124 of whom were evaluated with ultrasound, noting 12 CVC-related femoral DVTs.<sup>10</sup>

The incidence of asymptomatic CVC-related thrombosis, in prospective observational studies at the subclavian site, documented with ultrasound, ranges from 10.5% to 15.6%.<sup>11,12</sup> More liberal estimates obtained from venographic studies range from 24.2% to 50%.<sup>12-14</sup> The incidence of CVC-related internal jugular (IJ) thrombosis ranges from 4%, in a retrospective review of retrograde catheterizations,<sup>15</sup> to 41.7%, in a large prospective study utilizing ultrasound confirmation within 24-hr of catheter removal.<sup>11</sup> The authors of the latter study documented thromboses in 33% of cases (10% and 42% at the subclavian and IJ sites, respectively). However, they noted occlusive thrombi in only 3%<sup>11</sup> and observed that events were rarely clinically apparent. Factors independently associated with CVC-related thrombosis included the IJ site, age greater than 64 yr, and therapeutic heparinization.<sup>11</sup> Using ultrasound, Martin *et al.*<sup>16</sup> studied 60 patients with single lumen polyurethane catheters, inserted for an average of 15 days, and documented CVC-related axillary vein thrombosis in 11.6% of patients. In this study, the risk of thrombosis increased with canulation periods exceeding six days.<sup>16</sup>

Limited information is available pertaining to the incidence of thrombotic complications associated with peripherally inserted central catheter (PICC) access. Estimates vary widely, from 0.3%<sup>17,18</sup> to 56%,<sup>18</sup> with the largest retrospective reviews supporting incidence rates of 2.5% and 3.9% (2,063 and 813 PICC insertions, respectively), confirmed by ultrasound<sup>19,20</sup> and/or venography.<sup>19</sup> In a multivariate analysis, Grove *et al.*<sup>20</sup> noted that only catheter diameter was predictive of thrombosis, with thrombosis rates of 1%, 6.6%,

and 9.8% for 4-French (F), 5-F, and 6-F catheters, respectively. Chemaly *et al.*<sup>19</sup> noted a time-dependent relationship to PICC-associated thrombosis with 34%, 55%, and 75% of events occurring by the end of the first, second, and third weeks after insertion, respectively. In this study, concomitant PE was diagnosed in 3.8% of patients.<sup>19</sup> Regression analysis revealed that a history of venous thromboembolism, young age, discharge to a skilled nursing facility, and amphotericin B treatment were independent risks for development of PICC-related thrombosis.<sup>19</sup> This retrospective study may have underestimated the incidence of PICC-related complications. Moreover, inclusion of a large number of patients with human immunodeficiency virus infection likely confounded age as an independent predictor of thrombosis.<sup>19</sup> While early PICC complications are related to vascular injury at the time of insertion, late complications can be attributed to patient or infusate factors.<sup>17</sup>

### Central venous catheter-related right heart thromboembolism

Central venous catheter-related thrombi can lead to life threatening complications including sepsis, RHTE, and PE. Right heart thromboemboli most frequently represent embolized DVT lodged in the RA or, less often, the right ventricle (RV). In addition, RHTE include thrombi on foreign bodies (CVC-related, pacemaker-related, or tumour-related) and develop *in situ* (with injury to the endothelium, surgical anastomoses, or implanted devices). Right heart thromboemboli may be highly variable in appearance. Classification schemes have been developed to describe the configuration and the site of attachment of RAT. The echocardiographic appearance of RHTE has been correlated with the probability for embolization and death. Type-A thrombi are highly mobile, worm shaped structures that can prolapse through the tricuspid orifice. Conversely, type-B thrombi are

adherent to the atrial or ventricular walls and originate locally, in association with foreign bodies or in structurally abnormal atria. While most CVC-related thrombi extending into the heart are type-A, case series suggest that type-B thrombi can result from CVC-induced, mechanical irritation of the atrial wall.<sup>21</sup> Pulmonary embolism and death are reported to occur with 98 and 40% of type-A and 42 and 4% of type-B RAT, respectively.<sup>1</sup>

Right atrial thrombi are suspected and described with increasing frequency. In one study, the incidence of right heart mural thrombi (Innominate-superior vena cava, superior vena cava-RA, and RA) on post-mortem inspection of 141 consecutive patients with CVC was 29%.<sup>22</sup> A more conservative estimate of RHTE (12.5%) was found by Gilon *et al.*<sup>23</sup> in a prospective study of 55 patients who were followed for up to six to eight weeks after CVC insertion. The authors found that RHTE were significantly associated with a catheter tip in the RA, and that concurrent infection, malignancy, procoagulant states, and structural abnormalities were risk factors for development of CVC-related RAT.<sup>23</sup>

### Risk for pulmonary embolism

Lower and upper extremity DVTs are common and associated with increased patient morbidity and mortality, largely attributable to PE. A meta-analysis found that the pooled estimate of prevalent DVT, among studies investigating patients with *suspected* PE from ventilation perfusion (V/Q) scans, was 18% (95% CI 15-20%).<sup>24</sup> This study noted higher prevalent DVT estimates in pooling the results of studies investigating patients with *proven* PE, by either positive angiography or high probability V/Q scans [36% (95% CI 22-52%) and 45% (95% CI 33-58%), respectively].<sup>24</sup> Recent investigations support that UEDVT and CVC-related DVT are associated with morbidity and appreciable risk of PE. An early post-mortem study supported that up to 18% of patients with massive fatal PE demonstrated evidence of upper limb thrombus.<sup>25</sup> A systematic review of 329 cases of subclavian or axillary thrombosis reported a 9.4% incidence of PE, with over half of cases confirmed by lung scan or angiography.<sup>26</sup> Prandoni *et al.*<sup>27</sup> documented PE in 36% of patients with UEDVT, using either high probability V/Q scans or angiography. Monreal *et al.*<sup>28</sup> investigated 30 UEDVT patients (including 10 UEDVT and 20 CVC-related events) with V/Q scans and demonstrated normal, indeterminate, and positive scans in 90%, 10%, and 0% of DVT patients, and in 13 (65%), two (10%), and four (20%) patients with CVC-related DVT. Using V/Q scans, these

authors later documented PE in 15.1% of patients with CVC-related UEDVT.<sup>29</sup> Four of 13 patients with high probability scans were symptomatic, and two patients died of massive PE. Central venous catheter-related PE occur more often with thrombi adherent to catheters (sleeve thrombi) compared to venous wall (mural thrombi).<sup>30,31</sup> In summary, PE occurs in up to one-third of patients with UEDVT and in 15 to 20% of those with CVC-related UEDVT.

### Association between PE and RHTE

Both the incidence and the importance of RHTE in patients with PE are evolving in the literature. In two cohort studies involving 200 and 130 patients with confirmed PE, RHTE were detected, primarily by transthoracic echocardiography (TTE), in 7 and 18% of subjects, respectively.<sup>31,32</sup> A postmortem study documented concurrent RHTE and PE in 6% of cases.<sup>33</sup> More recently, the International Cooperative Pulmonary Embolism Registry<sup>34</sup> reported RHTE in 4% of 1,113 patients with PE undergoing echocardiography. When compared to PE patients without RHTE, patients with RHTE (including three CVC and two pacemaker-related events) had significantly higher 14-day (11 *vs* 21%,  $P = 0.032$ ) and three-month (16 *vs* 29%,  $P = 0.036$ ) mortality. While an early meta-analysis of echocardiographically detected RHTE, with and without PE (including CVC-related events), suggested an overall mortality rate of 31%,<sup>35</sup> a more recent review supports a rate of 27.1%.<sup>36</sup> Whether the increased mortality of RHTE can be attributed to concomitant PE or to the treatments administered, and whether RHTE represents an independent risk for death, remain to be elucidated. Notwithstanding, RHTE are associated with an appreciable risk for PE and death.

### Diagnosis of RHTE and PE in patients with hemodynamic compromise

Similar to patients without a CVC, if PE is suspected in a hemodynamically unstable patient with a CVC, in the absence of contraindications, anticoagulation should be initiated as soon as possible. Investigations, including Doppler ultrasound of the lower extremities and upper extremities, can be performed at the bedside. If the patient can be transported, alternate initial investigations, including a chest computed tomography or ventilation/perfusion (VQ) scan, can be performed.<sup>6</sup> If an investigation confirms the presence of clot, anticoagulation should be continued and an echocardiogram should be ordered. The purpose of echocardiography is to examine for evidence of RV dysfunction, RV dilatation, and RHTE. In the

presence of a normal RV and a high clinical index of suspicion, further definitive investigation with pulmonary angiography may be considered, but may not be feasible if patient transportation is required.<sup>6</sup>

Transthoracic echocardiography can evaluate RV size and RV function and can assess for the presence of RHTE. However, compared to TEE, the sensitivity of TTE in detecting RHTE is approximately 50-60%.<sup>37</sup> In case series, the false negative rate of TTE compared to TEE is as high as 60%.<sup>38</sup> Transthoracic echocardiography may miss RAT in patients with congenital heart disease and in patients following intracardiac surgery<sup>39</sup> and may underestimate clot size in those with RAT.<sup>37</sup> Consequently, TEE is preferred, as it permits more accurate determination of RV dimensions and better characterization of the location, appearance, and age of intracardiac thrombi.

### Prevention of CVC associated thrombosis

A recent meta-analysis of anticoagulation prophylaxis strategies in patients with CVCs summarized the results of 15 randomized trials evaluating low-dose, unfractionated, heparin infusions; oral, fixed, low-dose, vitamin-K antagonists; or subcutaneous, low-molecular-weight heparin administration.<sup>40</sup> The authors found that all prophylactic strategies significantly reduced the risk of all (symptomatic and asymptomatic) catheter-associated DVT, with summary relative risks ranging from 0.31 (95% CI, 0.13 to 0.71) for low-dose, unfractionated, heparin infusions; 0.37 (95% CI 0.26 to 0.52) for low-dose, vitamin-K antagonists; and 0.72 (95% CI 0.57 to 0.90) for subcutaneous low-molecular-weight heparin, without significantly increasing the risk of major bleeding. While all strategies provided effective prophylaxis against all (symptomatic and asymptomatic) catheter-associated DVT, individually, and against the risk of symptomatic DVT, collectively, no single strategy decreased the risk for development of symptomatic DVT. Moreover, amidst few events and trials reporting outcomes such as PE and mortality, the authors did not detect significant reductions in PE or death with anticoagulant prophylaxis.<sup>40</sup>

### Treatment of RHTE and PE

While RHTE are associated with PE and increased mortality, their management has not been well delineated. At present, the seventh American College of Chest Physicians Consensus Conference on Antithrombotic and Thrombolytic Therapy does not address the treatment of CVC-related PE and RHTE.<sup>41</sup> Heparin is not widely endorsed as a treatment option for RHTE and PE, given its slow onset of action and the im-

nent threat of significant PE. A large registry and a small RCT support that the mortality of patients with RHTE and PE, treated with intravenous heparin, was no different from that of untreated patients.<sup>34,42</sup> Treatment options for hemodynamically significant PE, associated with RV dilation or dysfunction, include surgery, thrombolysis, and catheter-directed embolectomy and fragmentation. Catheter removal mandates careful consideration of the potential for clot dislodgement and distal embolization. Inferior vena cava filter insertion should be considered to prevent recurrence in 'at risk' and critically-ill patients. Treatment decisions should be individualized.

### Surgery

The advent of extracorporeal circulation has reduced the morbidity and the mortality associated with cardiac surgery.<sup>43</sup> Notwithstanding, surgical embolectomy requires unstable patients to be exposed to the risks of thoracotomy and cardiopulmonary bypass. Consequently, variable mortality estimates (7% to 29.2%) associated with surgical embolectomy can be found in the literature.<sup>1,34,42</sup> In a non randomized study, Gulba *et al.*<sup>44</sup> assigned 37 patients with clinically suspected massive PE and shock to undergo either embolectomy or thrombolysis. The authors found survival rates of 77 and 67% favouring embolectomy, but acknowledged that a strong argument could be made for thrombolysis, given the limitations imposed by surgical availability. Similarly, early literature supported surgery for type-A RAT, but recognized that patient suitability and available surgical facilities were limiting factors. Current opinion and evolving literature favour maximizing medical therapy over early surgical intervention for most patients with significant PE.<sup>45</sup> Surgery remains part of the therapeutic armamentarium for RHTE with PE, especially with contraindications to thrombolysis, thrombolytic or heparin failure, large RHTE, or tricuspid valve occlusion.

### Systemic thrombolysis

Thrombolysis for acute PE thrombi may result in early improvement in hemodynamic status, gas exchange and RV function, while decreasing the likelihood of developing chronic pulmonary hypertension. Recognized indications for thrombolysis, in the setting of PE, include hemodynamic instability and echocardiographic demonstration of acute RV dysfunction.<sup>46</sup> Systemic thrombolysis has been the most extensively and the most rigorously evaluated treatment option for submassive and massive PE. Commonly used thrombolytic agents include streptokinase, urokinase, and recombinant tissue plasminogen activator (rTPA).

Thrombolytic agents activate plasminogen to form plasmin, which in turn cleaves fibrin and fibrinogen, as well as factors V and VIII. Recombinant tissue plasminogen activator has greater affinity for plasminogen when fibrin is present.<sup>47,48</sup> Recombinant tissue plasminogen activator is typically infused over two hours, compared to a 12-hr infusion with streptokinase and up to 24 hr of administration with urokinase. Evidence from RCTs, reporting on patients with massive<sup>49-54</sup> and submassive<sup>52,55</sup> PE, favour thrombolysis over heparinization. Randomized controlled trials comparing streptokinase and alteplase, in massive PE,<sup>56,57</sup> and urokinase and rTPA<sup>58</sup> failed to demonstrate superiority of one thrombolytic over another. The major risks associated with pulmonary thrombolysis include bleeding, hematoma formation at puncture sites, and intracranial hemorrhage, with intracranial hemorrhage occurring in approximately 2% of patients, ensuing up to 14 days following thrombolysis.<sup>59</sup> Death following thrombolysis for RHTE, due to migration of intra-cardiac thrombi prior to complete lysis, has been reported.<sup>60</sup> Thrombolysis should be carefully considered in postoperative patients, because the mortality of acute life threatening PE usually outweighs the risk of bleeding.<sup>61</sup>

An early meta-analysis<sup>35</sup> and a recent systematic review<sup>36</sup> and international registry<sup>34</sup> compared outcomes in patients with RHTE treated with surgery and thrombolysis. The meta-analysis included 119 patients with echocardiographically detected RHTE, with and without PE, and including CVC-related events, reported an overall mortality of 31% (39% without, and 28% with, a heart wall attachment site).<sup>35</sup> Variables significantly related to survival included concurrent PE and the treatment administered, with embolectomy and thrombolysis being of similar but inferior efficacy compared to heparin. This finding likely reflects selection bias, as hemodynamically stable patients were likely treated with heparin. Regardless of the treatment received, survival in patients with RHTE and PE was lower than in patients without PE, with survival rates of 70, 62, 62, and 19%, and 92, 89, 89, and 53%, respectively, with heparin, thrombolysis, embolectomy, and no treatment. Bias may also have resulted in selection of the best candidates for surgery. Conversely, a later systematic review involving 177 patients with RHTE, excluding CVC-related events, demonstrated that mortality was lowest with thrombolysis (11.3%), intermediate with surgical embolization (23.8%), and highest with anticoagulation alone (28.6%).<sup>36</sup> This study found a significant protective effect of thrombolysis [OR 0.33 (95% CI 0.11 to 0.98)] compared to surgery and endovascular inter-

ventions [OR 0.86 (95% CI 0.32 to 2.29)] on mortality, with anticoagulation serving as the reference group.<sup>36</sup> In a subgroup analysis of 123 patients, the authors found an increased risk of death with surgical interventions compared to thrombolysis [OR 2.83 (95% CI 1.04 to 7.69)].<sup>36</sup> More recently, Torbicki *et al.*<sup>34</sup> reported 14-day and three-month mortality in 42 and 1,071 PE patients, with and without RHTE. In addition to demonstrating significantly higher 14-day (11 *vs* 21%,  $P = 0.032$ ) and three-month (16 *vs* 29%,  $P = 0.036$ ) mortality with PE and RHTE, the authors noted 14-day (23.5, 20.8, and 25.0%) and three-month mortality rates (29.4, 29.2, and 25.0%) with heparin, thrombolysis, and embolectomy among patients with RHTE. The 14-day and three-month mortality figures for patients without RHTE, at corresponding times, were (8.0, 17.1, and 28.6%) and (14.3, 20.7, and 35.7%) with heparin, thrombolysis, and embolectomy, respectively.

For type-A clots, with and without PE and CVC, successful treatment with thrombolytics has been reported in the literature; however, caution is advised when treating type-B clots, as attachments may be destroyed during thrombolysis, resulting in clot dislodgement and PE. While a meta-analysis,<sup>35</sup> systematic review,<sup>36</sup> and registry<sup>34</sup> describe outcomes of patients with RHTE treated with thrombolysis, evidence in support of thrombolysis for CVC-related RAT is limited to case reports.

#### *Catheter-directed thrombolysis*

While evidence from observational studies<sup>62-65</sup> and one RCT<sup>66</sup> supports catheter-directed thrombolysis for isolated lower extremity DVT<sup>66-69</sup> and combined upper and lower extremity DVT,<sup>62</sup> evidence in support of catheter-directed thrombolysis for PE is limited. One case report<sup>67</sup> and a case series<sup>68</sup> of 13 postoperative patients, treated with reduced dose urokinase and heparin titrated to fibrinogen, describe successful catheter-directed thrombolysis for PE. An RCT comparing intravenous and intrapulmonary rTPA administration for treatment of massive PE found no advantage of intrapulmonary administration.<sup>69</sup> Moreover, in patients with RHTE, insertion of a CVC or Swan Ganz catheter to facilitate catheter-directed thrombolysis should be avoided, as clot dislodgement may be precipitated. An additional concern of catheter-directed thrombolysis, in the presence of RHTE, is the potential for fibrinolysis at the catheter tip resulting in dislodgement of suspended clots before dissolution. No study has directly compared catheter-directed and systemic thrombolysis for the management of RHTE and PE.

### Novel approaches

New approaches to management of PE are being reported. For PE with RHTE, case reports and case series have documented resolution of RAT using a glycoprotein IIb/IIIa receptor antagonist (abciximab) with concurrent heparin administration<sup>70</sup> and endovascular embolectomy with basket retrieval through a femoral approach, respectively.<sup>71,72</sup> Catheter thrombectomy, with<sup>73</sup> or without<sup>74-77</sup> local thrombolysis, has been shown to permit rapid RV recovery following fragmentation. Advantages of the latter strategy include avoidance of major surgery in high-risk patients and a decreased risk of bleeding. Notwithstanding, broader future application of these techniques may be limited by the requirement for specialized skills and equipment.

### Conclusion

Central venous catheter-related thrombosis occurs frequently and is an important source of morbidity and mortality for affected patients. Pulmonary embolism occurs in up to one-third of patients with UEDVT and in approximately 15% of patients with CVC-related UEDVT. Right heart thromboemboli, while infrequent, are associated with an appreciable risk for PE and death. Doppler ultrasound of the extremities and transesophageal echocardiography are key components of the diagnostic algorithm for suspected PE in unstable patients. Surgery and thrombolysis have been shown to enhance survival in patients with RHTE and PE. In the absence of contraindications, thrombolysis represents a convenient treatment option for patients with PE and hemodynamic compromise or RV failure. Type-A right RAT, due to their propensity to embolize, represent an additional, potential indication for thrombolysis.<sup>78</sup> Cardiac surgery should be considered for patients with contraindications to thrombolysis, thrombolytic failure, large RHTE, tricuspid occlusion, and a patent foramen ovale.<sup>79</sup> Notwithstanding, important considerations, including clot size, morphology and mobility, current or pre-existing PE, cardiopulmonary reserve, comorbidities, and the availability of local surgical and percutaneous expertise mandate that treatment be individualized.

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