Superior vena cava obstruction due to total implantable venous access devices in cystic fibrosis: Case series and review

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1. Educational aims

The educational aims of this manuscript are to

- Highlight various clinical presentations of TIVAD associated SVCO
- Discuss strategies for prevention of TIVAD associated SVCO
- Discuss strengths and weakness of the diagnostic and treatment modalities available for treatment of TIVAD associated SVCO.

2. Introduction

People with cystic fibrosis (CF) require frequent treatment with parenteral antibiotics for infective exacerbations of the associated bronchiectasis. Recurrent venous cannulation may be complicated by thrombosis of peripheral veins, which eventually limits venous access options. Totally implantable venous access devices (TIVADs) offer long term central venous access, but they may also be complicated by infection and thrombosis. TIVAD associated venous thrombosis rates between 0 and 13.6% have been reported (Table 1), but superior vena cava obstruction (SVCO) is a very rare occurrence. We present the largest case series to date of TIVAD associated SVCO, in patients with CF, and discuss possible risk factors, preventative strategies, and treatment approaches.

3. Case series

Between February 2008 and December 2009 sixty (24%) of the 251 patients attending our adult CF centre had a TIVAD in situ and during this period five individuals (8%) developed symptomatic SVCO (Table 2). In four patients the TIVAD had been inserted at another hospital (2 overseas general surgical units, 1 paediatric CF centre, 1 interstate hospital), which employ different insertion techniques and catheter types to our own practice. The cases are discussed in greater detail to highlight important clinical features and potential management strategies.

3.1. Case 1

A 16 year old female, with severe lung disease presented with facial swelling and worsening breathlessness 19 months after the insertion of her third TIVAD (2 removed previously; 1 suspected infection, 1 blocked). Initial colour flow Doppler ultrasound (CDUS) demonstrated normal compressible upper extremity veins. However, due to ongoing symptoms computed tomography venography (CTV) was performed which demonstrated occlusive...
thrombus surrounding the tip of the TIVAD at the level of the mid SVC (Fig. 1a). Endovascular thrombus aspiration was attempted, but abandoned due to severe coughing. She was transferred to the intensive care unit and underwent TIVAD directed thrombolysis with alteplase 46, an initial bolus of 2.5 mg was administered, followed by an infusion of 0.5 mg/h over a 72 h period. Her gas exchange and cardiovascular status remained stable throughout the infusion. Thrombolysis resulted in total symptomatic resolution. A repeat CTV demonstrated partial recannulisation of the SVC, with no evidence of secondary pulmonary emboli (Fig. 1b). Thrombolytic was continued without complication up to the intermittent blockage, and a new left sided chest TIVAD inserted.

A 31 year old female who had a left sided TIVAD inserted at an interstate hospital, presented to the same hospital nine months later due to respiratory failure. A CTV demonstrated almost complete occlusion of the mid SVC (Fig. 3a). Anticoagulation with heparin was immediately commenced with IV heparin followed by an infusion of 0.5 mg/h over a 72 h period. Her gas exchange and cardiovascular status remained stable throughout the infusion. Thrombolysis resulted in total symptomatic resolution. A repeat CTV demonstrated partial recannulisation of the SVC, with no evidence of secondary pulmonary emboli (Fig. 1b). Thrombolytic was continued without complication up to the intermittent blockage, and a new left sided chest TIVAD inserted. Anticoagulation was continued without complication up to the patient’s death six months later due to respiratory failure.

### Table 1
TIVAD related venous thrombosis rates in patients with CF published over the last 20 years.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of TIVADs</th>
<th>Duration of follow-up</th>
<th>No. of symptomatic Thromboses</th>
<th>No. of episodes of SVCO</th>
<th>Anticoagulated</th>
<th>Thrombolysed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Royle et al.1</td>
<td>165</td>
<td>20 years</td>
<td>5 (3%)</td>
<td>0</td>
<td>5/N/R</td>
<td>5/N/R</td>
</tr>
<tr>
<td>Munck et al.2</td>
<td>452</td>
<td>8 years</td>
<td>21 (47%)</td>
<td>N/R</td>
<td>2/N/R</td>
<td>5/N/R</td>
</tr>
<tr>
<td>Atken and Tonelli3</td>
<td>85</td>
<td>10 years</td>
<td>14 (16%)</td>
<td>3</td>
<td>8/N/R</td>
<td>0</td>
</tr>
<tr>
<td>Kariyawasam et al.4</td>
<td>115</td>
<td>13 years</td>
<td>4 (3.5%)</td>
<td>3</td>
<td>4/N/R</td>
<td>0</td>
</tr>
<tr>
<td>Deerojanawong et al.5</td>
<td>57</td>
<td>9 years</td>
<td>5 (9%)</td>
<td>5</td>
<td>5/N/R</td>
<td>5/N/R</td>
</tr>
<tr>
<td>Rodgers et al.6</td>
<td>61</td>
<td>8 years</td>
<td>4 (7%)</td>
<td>0</td>
<td>4/N/R</td>
<td>3</td>
</tr>
<tr>
<td>Burdon et al.7</td>
<td>75</td>
<td>5 years</td>
<td>0 (0%)</td>
<td>0</td>
<td>0/N/R</td>
<td>0</td>
</tr>
<tr>
<td>Sola et al.8</td>
<td>22</td>
<td>6 years</td>
<td>3 (14%)</td>
<td>0</td>
<td>0/N/R</td>
<td>0</td>
</tr>
<tr>
<td>Yung et al.9</td>
<td>33</td>
<td>8 years</td>
<td>3 (9%)</td>
<td>3</td>
<td>0/N/R</td>
<td>0</td>
</tr>
<tr>
<td>Morris et al.10</td>
<td>68</td>
<td>4 years</td>
<td>0 (0%)</td>
<td>0</td>
<td>0/N/R</td>
<td>0</td>
</tr>
<tr>
<td>Garwood et al.11</td>
<td>47</td>
<td>12 years</td>
<td>3 (6%)</td>
<td>0</td>
<td>0/N/R</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1180</strong></td>
<td><strong>62 (5%)</strong></td>
<td><strong>12 (1%)</strong></td>
<td><strong>3</strong></td>
<td><strong>3</strong></td>
<td><strong>3</strong></td>
</tr>
</tbody>
</table>

TIVAD: Totally implantable venous access device; SVCO: superior vena cava obstruction; N/R: not reported.

3.2. Case 2

A 23 year old female, with a right sided chest TIVAD in situ for 7 years was admitted for an elective surgical procedure. She was using depo provera contraception. On initiation of preoperative intravenous hydration she developed upper limb and facial swelling. Digital subtraction venography (DSV) demonstrated thrombus around the catheter obstructing the SVC. A portogram revealed normal flow through the catheter. Magnetic resonance venography (MRV) confirmed thrombus extending along the brachiocephalic vein to confluence of SVC. Surgery under general anaesthesia was performed without complication and intravenous heparinisation was commenced immediately post-operation, followed by therapeutic anticoagulation with warfarin (target INR 2.0–3.0) was commenced. The TIVAD was removed after six months due to intermittent blockage, and a new left sided chest TIVAD inserted. Anticoagulation was continued without complication up to the patient’s death six months later due to respiratory failure.

#### 3.3. Case 3

A 31 year old female who had a TIVAD inserted at an interstate hospital, presented to the same hospital nine months later with acute pancreatitis and dehydration. On initiation of intravenous fluids, she developed symptoms of throat tightness, accompanied by facial and upper limb swelling. She had commenced the oral contraceptive pill (OCP) two months prior to presentation. DSV and a portogram demonstrated reduced line patency with narrowing of the SVC distal to the catheter tip. Anticoagulation with heparin (7 days) followed by warfarin was commenced. The line was left in situ. On admission to our centre four months later for elective cholecystectomy, she continued to experience significant symptoms of SVCO. MRV demonstrated a high grade stenosis of the SVC (max diameter of 4 mm) (Fig. 2a). Balloon angioplasty was performed followed by TIVAD removal. Two months later she had continued and substantial improvement in symptoms and a repeat MRV demonstrated improved patency of the SVC (max diameter of 10 mm) (Fig. 2b).

#### 3.4. Case 4

An 18 year old female presented with an infective exacerbation of CF and dehydration two weeks following a 4 h flight from New Zealand to Australia. A TIVAD had been inserted in New Zealand three months prior to presentation. She had also commenced the OCP three weeks prior to presentation. On initiation of intravenous hydration she developed facial swelling and throat tightness. CTV demonstrated the TIVAD tip to be located at the confluence of the brachiocephalic vein, with adherent clot extending distally, and almost complete occlusion of the mid SVC (Fig. 3a). Anticoagulation was immediately commenced with IV heparin followed by warfarin. Serial CTV’s over the next four months demonstrated progressive reduction in clot size (Fig. 3b) and the TIVAD was then removed without complication with cessation of warfarin. Twelve months following TIVAD removal the patient remains asymptomatic. When requiring intravenous access a mid-line peripheral catheter has been inserted under ultrasound guidance with the tip positioned in the axillary vein and removed at the end of each hospitalisation.

#### 3.5. Case 5

A 31 year old female who had had a left sided TIVAD inserted nine months previously (right sided insertion not technically possible) was noted by her carer to have developed prominent collateral veins on her anterior chest wall. She had a background history of moderate lung disease, epilepsy, and intellectual impairment. A CTV revealed left subclavian vein narrowing with catheter tip associated thrombus in the SVC. Given the absence of symptoms and previous difficulty obtaining venous access the TIVAD was left in situ. Prophylactic warfarin was commenced (INR range 1.5–2.0). Currently, five months later the TIVAD continues to
function satisfactorily and she remains asymptomatic with no bleeding complications.

4. Discussion

To our knowledge this is the largest reported series of SVCO associated with TIVADs in patients with CF.

The explanation for the higher incidence of SVCO compared to previously reported series is not immediately apparent. Post-insertion care and maintenance of TIVADs at our centre is in line with that of other large CF centres worldwide. It is noteworthy that three of the TIVADs were inserted in other hospitals that perform this procedure infrequently, raising the possibility that operator experience may be a contributory factor. Given the year long high ambient temperatures in Queensland (in Brisbane the annual mean maximum temperature is 26.5 °C, and mean minimum temperature is 16.2 °C) there is a high risk of dehydration in patients with CF, which may increase the risk of thrombosis in this particular population. It is also noteworthy that all five of the patients in the case series were female and three of them were on some form of hormonal contraception. Finally it is possible that previous authors may have mis-classified SVCO as symptomatic thrombosis.

The cases highlight a number of important lessons in the prevention, diagnosis, and treatment of catheter associated SVCO and potentially represents another important morbidity associated with increased life span for adults with CF.

4.1. Risk factors for thrombosis

4.1.1. Oral contraceptives

The OCP is associated with spontaneous deep vein and upper extremity thrombosis, and is likely to increase the risk of central line related thrombosis. The risk may be lessened but not ameliorated with progesterone only pills. The World Health Organisation (WHO) guidelines on contraception state that systemic oestrogen-based contraception poses an unacceptable health risk in people who have previously suffered venous thrombo-embolism, as well as in those with an ongoing increased thrombogenic risk (a category into which patients with TIVADs may arguably be included). The WHO favours the use of intrauterine devices (either copper or drug eluting), barrier devices, or progesterone only pills in this circumstance.

4.1.2. Line related factors

Correct catheter placement is important in reducing the risk of thrombosis. In a previously reported series of 379 patients with a TIVAD for cancer chemotherapy, ten episodes of venous thrombosis occurred. In nine of these cases, the catheter tip was positioned in the upper one-third of the SVC and 50% had evidence of SVC narrowing on the plain chest radiograph. These findings were replicated in a prospective study which demonstrated a thrombosis rate of 46% for correctly versus 6% for incorrectly inserted catheters. Local endothelial trauma by the catheter tip may predispose to thrombus formation, but other factors may include; the catheter material (polyurethane catheters being found to be the least thrombogenic compared to silicone, polyethylene, or Teflon coated lines); catheter diameter (greater risk with larger diameter); and catheter placement in the left subclavian vein because of the more acute anatomical course into the SVC.

4.1.3. Thrombophilia

There are two published studies on the rate of thrombophilia in patients with CF. Both studies reported that patients with CF have higher rates of thrombophilia on testing than control populations. The authors therefore recommended thrombophilia...
screening prior to TIVAD insertion, although neither study actually demonstrated any correlation with the prevalence of line-associated thrombosis.

These recommendations need to be viewed with caution, as thrombophilia testing abnormalities in CF are often transient and related to the acute phase response, similar to the abnormalities observed in anti-phospholipid antibody and protein C levels in some CF patients when unwell.19

4.1.4. Dehydration

Dehydration can be a major problem in patients with CF, especially during infective exacerbations in sub-tropical and tropical climates. The associated haemoconcentration may represent a significant risk factor for venous thrombosis.20

4.1.5. Author’s practice

We counsel female patients on the risks associated with systemic hormone based contraceptive prior to TIVAD insertion and observe the WHO recommendations where possible by switching patients from systemic oestrogen-based contraception. Our centre currently inserts small diameter (8 French), polyurethane TIVAD catheters. Depending on the preferred location of the injection port these may be inserted surgically (chest) or radiologically (arm), with the catheter tip sitting in the lower one-third of the SVC. In the absence of a family history of thrombosis we do not perform routine thrombophilia screening prior to TIVAD insertion. Patients with TIVADs are aggressively rehydrated when admitted for treatment of exacerbations or elective surgery.

4.2. Investigation of SVC obstruction

A number of imaging modalities are available for the investigation of SVCO.

4.2.1. Colour flow Doppler ultrasound

Sensitivity and specificity rates of 94% and 96% respectively have been reported with CDUS for the diagnosis of symptomatic catheter related upper extremity venous thrombosis.21 This accuracy, combined with its safety and wide availability, makes CDUS the investigation of first choice. However, as highlighted in case 1, CDUS can produce false negatives due to difficulty in obtaining suitable acoustic windows to visualise the SVC, and should not be considered sufficient on its own to exclude thrombosis when clinical suspicion is high.

4.2.2. Digital subtraction venography

DSV is the gold standard for assessing upper extremity thrombosis and is widely available in most radiological departments. However, it is of limited use in up to 20% of cases due to difficulty...
obtaining venous access (particularly in the presence of upper limb oedema), and the small risk of contrast allergy. The other drawbacks of DSV are the need to perform bilateral venopunctures to completely map the upper extremity vasculature, and failure to visualise the internal jugular vein.

4.2.3. Computed tomography venography and magnetic resonance venography

CT and MRI based techniques have the advantage of imaging the entire upper extremity vasculature in one scan session which allows assessment of the site of obstruction and planning of future potential vascular access sites. Multi-slice detector CT scanners provide rapid image acquisition and excellent resolution of the intravascular thrombus and the degree of vessel stenosis, when compared to conventional CT scans. The major limitation of CT imaging is the requirement for IV contrast and radiation exposure.

Both non-contrast and gadolinium enhanced MRV have been shown to be sensitive in detecting SVC obstruction. Gadolinium enhancement provides the advantages of faster image acquisition and less artefact. However gadolinium nephrotoxicity limits its use in patients with renal impairment. Techniques currently in development may allow significant gadolinium dose reduction and wider applicability. A major limitation of MRV is its limited availability outside of major radiology centres.

4.2.4. Authors practice

We base our choice of imaging modality on the individual case presentation. Where endovascular procedures are considered we favour the use of MRV. We recommend that if clinical suspicion of SVCO is high that a normal CDUS is not considered sufficient to exclude the diagnosis.

4.3. Prophylaxis and treatment of thrombosis

Prospective studies into the optimum management of line related thrombosis are limited, with the majority of recommendation based on small numbers of studies or extrapolated from studies in patients with cancer.

4.3.1. Prophylactic antiplatelet/anticoagulation therapy

Following a retrospective audit of TIVAD complications in patients with CF which demonstrated a thrombosis rate of 13.6% Sola et al. recommended a policy of initiating all patients with a TIVAD on aspirin, however the authors have not reported the impact on rates of thrombosis. There is low level evidence available that suggests low dose anticoagulation is beneficial in preventing line related thrombosis in patients with cancer, however there are no similar studies published in patients with CF.

The potential risk of routine anticoagulation in CF is haemoptysis. The rate of massive haemoptysis in patients with CF is approximately 1 per 100 patient years and most often occurs in patients with severe lung function impairment (the patient group most likely to require a TIVAD) and is associated with increased decline in lung function and mortality.

4.3.2. Therapeutic anticoagulation

The optimum treatment protocol for catheter related thrombosis remains controversial. Guidelines published by The American College of Chest Physicians (ACCP) recommend that patients should be anticoagulated for a 3–5 day period initially with heparin, followed by removal of the line if it is no longer required and three months of anticoagulation. Where ongoing venous access is required they recommend that the line may remain in situ, but that a longer period of anticoagulation should be considered, although this may be reduced to prophylactic doses after the initial three months.

4.3.3. Thrombolysis

Catheter directed thrombolysis has been shown to effectively restore vessel patency if delivered early after clot development but studies have been limited to very small numbers of patients, and varied in thrombolytic regimen employed. Thrombolysis has not been shown to be superior to anticoagulation alone in the longer term. The ACCP therefore recommends that thrombolysis be limited to those with recent onset of severe symptoms and only be undertaken in centres with adequate expertise.

4.3.4. Endovascular and surgical intervention

There are no prospective trials comparing endovascular procedures to medical therapy in benign SVC. A benign cause was identified in 14 of 52 patients included in a series of patients treated with endovascular stenting for persistent SVC despite medical treatment. All 14 were successfully treated, with no reported complications, however six required a second endovascular procedure during the follow-up period. There have, however been case reports of stent migration with associated morbidity and mortality. Endovascular clot retrieval has been reported to be successful in isolated case reports only. The ACCP recommend that endovascular procedures only be performed in specialised centres.
and only in selected cases where conservative treatment has failed.27

Rizvi et al. compared endovascular stenting to surgical recon-
struction in 70 patients with severe, symptomatic SVCO despite
anticoagulation. Surgical reconstruction was associated with
significant morbidity, and the authors advocated stenting as the
preferred therapeutic option.32

4.3.5. Authors practice

There is currently no data to support the role of prophylactic
anticoagulation and we therefore do not initiate this routinely.
Following symptomatic thrombosis, we initiate therapeutic anti-
coagulation with warfarin (INR 2–3) for three months, followed by
low dose warfarin (INR 1.5–2.0) while the TIVAD remains in situ.
TIVAD removal is considered for ongoing significant symptoms of
SVCO, or when significant bleeding necessitates premature
discontinuation of anticoagulation. Thrombolysis and angioplasty
is considered in severely symptomatic patients and is carried out
with intensive care support. Although primary surgical recon-
struction is not advocated, in the second case the authors highlight
a novel surgical approach that was only possible at the time of lung
transplantation.

5. Conclusion

The TIVAD offers reliable long term venous access for patients
with CF who require repeated courses of intravenous antibiotics,
especially in patients with limited peripheral access options. To
minimize complications, expertise in line insertion and mainte-
nance is paramount. There remains limited evidence to guide
clinicians in important management issues including thrombo-
ophilia screening and prophylactic anticoagulation, and multi-centre
randomised controlled trials to address these issues would be
beneficial.

Conflict of interest statement

This was an unfunded review.
None of the authors have any conflict of interest to declare.

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invaluable in reducing complication rates.

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