Subclavian vein thrombophlebitis: complication of total parenteral nutrition (TPN)

A retrospective analysis of 1311 patients who underwent 1611 central venous catheterizations for total parenteral nutrition (TPN) showed clinical subclavian and central venous thrombophlebitis in 11 patients (0.8%). Catheter-related complications occurred in 9.6% of the patients. Of 11 patients with thrombophlebitis, 10 were female, and half of the patients had ulcerative colitis or Crohn's disease. Fifty percent of the patients had multiple punctures and catheter malposition. In 3 patients the diagnosis of central venous thrombophlebitis was made within four days, and in 6 patients, within two to four weeks of catheter insertion. The initial symptoms in 81% of the patients were fever, chills, diaphoresis, and severe pain including the arm, axilla, neck, and pectoral areas followed by edema and superficial collateral venous distention. Internal jugular occlusion in 5 patients, extension into the superior vena cava in 5 patients, and right atrium involvement in one patient were noted. Staphylococcus bacteremia was documented in 6 patients with the onset of symptoms. There was one fatality due to pulmonary embolism. Eight patients are alive and well and 2 of them have chronic edema of the arm. Two patients died of causes unrelated to subclavian vein thrombosis or TPN.

Index terms: Parenteral feeding • Subclavian vein • Thrombophlebitis

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The technique of percutaneous subclavian venous catheterization was reported by Aubaniac in 1952, for the rapid administration of intravenous fluids for patients in shock. In 1962, Wilson, in this country, introduced the same method for the measurement of central venous pres-
Table 1. Complication of subclavian vein catheterization for total parenteral nutrition

<table>
<thead>
<tr>
<th>Author, yr, no. of published cases, complications, %</th>
<th>Pneumothorax</th>
<th>Catheter malposition</th>
<th>Hemothorax</th>
<th>Hydrothorax</th>
<th>Arterial puncture</th>
<th>Catheter sepsis</th>
<th>Hematoma or bleeding</th>
<th>Central venous thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christensen7 1967 (review series)</td>
<td>30</td>
<td>12</td>
<td>5</td>
<td>3</td>
<td>13</td>
<td>4</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Bernard8 1971</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ryan10 1974</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>14</td>
<td>1</td>
<td>7</td>
<td>5</td>
<td>10.4%</td>
</tr>
<tr>
<td>Present series</td>
<td>33</td>
<td>48</td>
<td>3</td>
<td>6</td>
<td>22</td>
<td>5</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Total 3408 cases</td>
<td>88</td>
<td>89</td>
<td>10</td>
<td>8</td>
<td>24</td>
<td>55</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>2.4%</td>
<td>2.6%</td>
<td>0.3%</td>
<td>0.2%</td>
<td>0.2%</td>
<td>0.7%</td>
<td>1.6%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

Catheterization of the subclavian vein is not without hazard. Incidence of the most common complications related to the initial catheter placement varies in the reported series from 4.6% to 39.4% (Table 1). Morbidity related to complications is low. Some unusual but serious complications are noted in Table 2.

Central venous thrombosis and septic thrombophlebitis are infrequent but potentially fatal complications of subclavian vein catheterization for total parenteral nutrition (TPN). During the last five years we have encountered 11 cases at the Cleveland Clinic. The purpose of this pres-
entation is to report the incidence of this complication, review the diagnostic features, clinical manifestations, and possible etiological factors in an effort to prevent, recognize, and adequately treat this complication.

Material and methods

The records of 1311 consecutive patients undergoing central venous catheterization for TPN from September 1975 through December 1980 were retrospectively reviewed to establish the incidence of complications related to catheter placement and maintenance. Eleven patients who developed subclavian and central venous thrombosis during the time they received TPN were identified and their charts reviewed.

During a period of 64 months a total of 1603 catheters involving 1311 patients were placed and closely monitored by the TPN team in our institution. Resident surgeons with the assistance of the hyperalimentation nurses inserted the 8" long radiopaque polyethylene catheter using sterile aseptic techniques at the bedside. The right infracavicular approach was preferred and used in 913 catheterizations (56.9%), the left in 549 (34.2%), the right internal jugular in 94 (5.8%), and the left internal jugular in 47 (2.9%). Free retrograde venous blood flow was always demonstrated before a slow infusion of an isotonic solution was administered to keep the line patent. A portable chest roentgenogram was obtained to confirm the proper placement of the catheter in the superior vena cava and to exclude any possible complications related to the catheter placement before infusion of the hyperalimentation solution. The central venous catheter was used exclusively for the TPN solution. No other fluids, drugs, blood, or blood products were administered through the line. Central venous pressure measurements were also not allowed. The TPN line was carefully attended. The skin was prepared with acetone and povidone iodine solution. Povidone ointment was placed over the insertion site. The occlusive dressing was routinely changed three times a week and the intravenous tubing was changed daily. One thousand units of heparin were added to each litre of TPN solution to reduce catheter thrombogenesis. The indications for TPN in 1311 patients are summarized in Table 3.

Results

The insertion of 1603 catheters in 1311 patients led to complications involving 7.8% of the catheters and 9.6% of the patients (Table 1). Multiple catheterizations were required in 326 patients (24.8%) and single catheterization was done in 985 patients (75.1%). Central venous thrombosis was clinically detected in 11 patients (0.84%). Difficult catheterization with multiple venipunctures occurred in 5 of 11 patients (45%). The clinical findings, diagnostic modalities, treatment, and morbidity and mortality of this group of patients receiving hyperalimentation are summarized in Table 4. There were 10 female patients and one male; ages ranged from 11 to 63 years. The most frequent indications for intravenous hyperalimentation were gastrointestinal tract disorders (10 patients); 6 had severe complications or acute mucosal ulcerative colitis or Crohn's disease. Three patients had radiation enteritis, one had extensive ischemic colitis, the other 2 had severe nutritional depletion, the first one suffering from Werner-Morrison syndrome, and the second had lost 15% body weight five weeks after open heart surgery.

The diagnosis was established in 5 patients three to nine days after the initial subclavian catheter insertion. It was characterized by the presence of temperature elevation greater than 102 °F in 9 patients (81%), tachycardia, chills, followed by edema of the involved extremity in 9 patients (81%), edema of the neck in 8 (72%), facial edema in 7 (63%), and ipsilateral, pectoral, and subclavian area edema in 4 patients (36%). Cyanosis of the involved extremity was seen in only 2 patients. Severe pain over the lateral aspect of the involved neck was observed in 9 patients (81%), axillary areas in 8 (72%), pectoral area in 7 (63%), and in the arm in 5 (27%). In 6 patients (54%) the clinical findings of central venous thrombosis appeared 20 to 40 days after the initiation of TPN. In 10 patients (91%) prom-
### Table 4. Clinical summary

<table>
<thead>
<tr>
<th>Case, age, sex</th>
<th>Diagnosis, complications</th>
<th>Technique of insertion</th>
<th>Single/multiple punctures</th>
<th>No. of days TPN</th>
<th>Fever</th>
<th>Edema</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 51 WF</td>
<td>Crohn's disease</td>
<td>Lt subclavian, infracavicular</td>
<td>Single</td>
<td>3</td>
<td>104 Chills</td>
<td>Arm, neck</td>
<td>Neck, arm</td>
</tr>
<tr>
<td>2 32 WF</td>
<td>Radiation enteritis, multiple fistulae</td>
<td>Rt subclavian, infracavicular</td>
<td>Single</td>
<td>19</td>
<td>101</td>
<td>Facial, lateral neck, rt arm</td>
<td>Severe, neck, axilla</td>
</tr>
<tr>
<td>3 55 WF</td>
<td>Ischemic colitis</td>
<td>Rt subclavian, infracavicular</td>
<td>Single</td>
<td>9</td>
<td>102</td>
<td>Facial, neck, chest, arms</td>
<td>Rt chest wall, neck</td>
</tr>
<tr>
<td>4 46 WF</td>
<td>Crohn's disease, retromastoidal fistula</td>
<td>Rt subclavian, lt internal jugular</td>
<td>Multiple, difficult</td>
<td>14</td>
<td>103</td>
<td>Chills</td>
<td>Severe, lt neck, chest wall, arm</td>
</tr>
<tr>
<td>5 63 WF</td>
<td>Active ulcerative colitis</td>
<td>Rt subclavian, infracavicular</td>
<td>Single</td>
<td>4</td>
<td>101</td>
<td>Rt lateral neck, chest wall, arm</td>
<td>Rt neck, axilla</td>
</tr>
<tr>
<td>6 60 WF</td>
<td>Werner-Morrison syndrome</td>
<td>Lt subclavian, infracavicular</td>
<td>Single</td>
<td>4</td>
<td>99</td>
<td>Lt arm, axilla</td>
<td>Lt axilla</td>
</tr>
<tr>
<td>7 32 WF</td>
<td>Ulcerative colitis with pelvic sepsis</td>
<td>Rt subclavian, infracavicular</td>
<td>Multiple, difficult</td>
<td>42</td>
<td>101</td>
<td>Rt neck, face, arm</td>
<td>Rt neck, axilla, shoulder</td>
</tr>
<tr>
<td>8 28 WM</td>
<td>Active Crohn's disease</td>
<td>Lt subclavian, infracavicular</td>
<td>Multiple</td>
<td>7</td>
<td>102</td>
<td>Chills</td>
<td>Lt neck, chest wall</td>
</tr>
<tr>
<td>9 53 WF</td>
<td>Radiation proctitis, sacral, decubitus</td>
<td>Rt/Lt subclavian, infracavicular</td>
<td>Multiple, difficult</td>
<td>24</td>
<td>102</td>
<td>Chills</td>
<td>Arms</td>
</tr>
<tr>
<td>10 54 WF</td>
<td>Cancer, cervix pelvic exenteration</td>
<td>Rt/Lt subclavian infracavicular</td>
<td>Multiple</td>
<td>36</td>
<td>103</td>
<td>Rt neck, chest, arm, face</td>
<td>Rt neck, chest, face, arm</td>
</tr>
<tr>
<td>11 11 WF</td>
<td>Postoperative congenital heart disease</td>
<td>Rt subclavian</td>
<td>Single</td>
<td>27</td>
<td>103</td>
<td>Chills</td>
<td>Rt neck, face, arm, chest</td>
</tr>
</tbody>
</table>

TPN = total parenteral nutrition, PE = physical examination, – = negative, IV = intravenous, + = positive, SVC = superior vena cava.

Persistent superficial collateral venous circulation over the deltoid and pectoral areas was detected within 24 to 48 hours, after the fever, edema, and tenderness over the pectoral and axillary area had been noted.

Persistent leukocytosis greater than 15,000/mm$^3$ with an increase in polymorphonuclear cells was present in 9 patients (81%). Peripheral blood cultures were obtained during the initial febrile episode that preceded the typical physical findings of central venous thrombosis. In 3 patients *Staphylococcus epidermidis* was isolated; in 3 others, *Staphylococcus aureus*. Routine culture of the catheter tip was done in 10 patients. Only 2 had a positive culture; patient 11 had rare *Staphy. aureus*, and peripheral blood cultures on this patient were sterile. The second, case 4, had multiple positive blood cultures for *Staphy. aureus*, which also was isolated from the catheter tip. Eventually, septic thrombophlebitis of the left subclavian, internal jugular, and innominate veins developed in this patient.

Bacteremia was documented in 2 patients before the initiation of TPN. A 63-year-old white woman (case 5) with active ulcerative colitis, heart failure, and a decubitus ulcer, had a *Staphy. aureus* bacteremia, which was treated with oxacillin, intravenously. However, Staphylococcus bacteremia was documented at the time of the central venous thrombosis. The second patient, case 3, a 55-year-old white woman with ischemic colitis, had one of two blood cultures positive for *Pseudomonas aeruginosa*, which was thought to be a contaminant.

Venograms were obtained in 9 patients (Figure) between two to eight days after the clinical diagnosis had been established. In all patients 90% to 100% thrombosis of the ipsilateral subclavian vein was demonstrated, with extension into the internal jugular in 7, the innominate, axillary,
<table>
<thead>
<tr>
<th>Venograms</th>
<th>Positive blood cultures</th>
<th>WBC count mm$^3$</th>
<th>Heparin U/day</th>
<th>Antibiotic</th>
<th>PE</th>
<th>Mortality/morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis, lt subclavian, axilla, jugular, innominate</td>
<td>4 positive S. aureus</td>
<td>24,000</td>
<td>30,000 IV</td>
<td>Nafcillin</td>
<td>+</td>
<td>Died, septic pulmonary and systemic emboli</td>
</tr>
<tr>
<td>Thrombosis, rt axilla, subclavian</td>
<td>2 positive S. epidermidis</td>
<td>15,000</td>
<td>30,000</td>
<td>Oxacillin, IV 12 gr</td>
<td>× 14 days</td>
<td>Died 3 wk later of heart failure</td>
</tr>
<tr>
<td>Rt subclavian, internal jugular, innominate</td>
<td>Negative</td>
<td>20,000</td>
<td>36,000</td>
<td>Cefazolin, IV 4 gr/day</td>
<td>× 14 days</td>
<td>Died suddenly 11 days after exploratory laparotomy</td>
</tr>
<tr>
<td>Lt subclavian, jugular thrombosis, extension into SVC</td>
<td>4 positive S. aureus</td>
<td>24,000</td>
<td>30,000 IV</td>
<td>Nafcillin</td>
<td>+</td>
<td>Died 3 wk later of heart failure</td>
</tr>
<tr>
<td>None</td>
<td>2 positive S. aureus</td>
<td>16,000</td>
<td>None</td>
<td>Oxacillin 8 gr IV/day × 14 days</td>
<td>× 14 days</td>
<td>Died suddenly 11 days after exploratory laparotomy</td>
</tr>
<tr>
<td>None</td>
<td>Negative</td>
<td>12,000</td>
<td>None</td>
<td>None</td>
<td>+</td>
<td>Died suddenly 11 days after exploratory laparotomy</td>
</tr>
<tr>
<td>Rt subclavian innominate, internal jugular, extension into SVC</td>
<td>Negative</td>
<td>16,000</td>
<td>30,000 IV</td>
<td>Cleocin, IV 600 mg × 3/day 10 days</td>
<td>× 2 wk</td>
<td>Died of heart failure</td>
</tr>
<tr>
<td>Lt subclavian and internal jugular veins</td>
<td>One S. aureus</td>
<td>14,000</td>
<td>30,000 IV</td>
<td>None</td>
<td>–</td>
<td>Well</td>
</tr>
<tr>
<td>Rt/lt subclavian, extension into SVC</td>
<td>S. epidermidis</td>
<td>9000</td>
<td>40,000 IV</td>
<td>Nafcillin, tobramycin</td>
<td>× 2 wk</td>
<td>Well</td>
</tr>
<tr>
<td>Rt internal jugular, subclavian, innominate</td>
<td>Negative</td>
<td>15,000</td>
<td>30,000 IV</td>
<td>Vancomycin</td>
<td>–</td>
<td>Well</td>
</tr>
<tr>
<td>SVC, rt/lt subclavian, internal jugular, extension into rt atrium</td>
<td>Negative</td>
<td>19,000</td>
<td>24,000 IV</td>
<td>Nafcillin, oxacillin</td>
<td>× 2 wk</td>
<td>Died of heart failure</td>
</tr>
</tbody>
</table>

and superior vena cava in 4. In an 11-year-old girl (case 11), who underwent a previous modified Fontan procedure for a complex congenital heart disease, a thrombus was found extending into the right atrium that was not present before initiation of hyperalimentation.

The venograms showed a prominent venous collateral pattern in all stages. When the subclavian vein was obstructed, the predominant collateral flow followed the cephalic-transverse, scapular-transverse, cervical-jugular vein route pattern "first rib bypass.** When the axillary vein was thrombosed, the venous collateral pattern followed the thoracic-intercostal-internal mammary vein route. Also, prominent and numerous small axillary venous vessels could be seen, bridging the length of the thrombosed axillary vein segment.

When the clinical diagnosis was established and venograms were obtained, systemic hepariniza-
tion (500 U/kg/24 hr) was administered in a continuous intravenous drip in 9 of 10 patients for ten to 14 days. Results of daily partial thromboplastin time studies were obtained to control the dose of heparin. Because of a hemothorax, the patient in case 6 was not heparinized. However, this woman was given Mini-Heparin (5000 units subcutaneously twice a day). She died suddenly 11 days after an exploratory laparotomy, possibly as a result of pulmonary embolism. Autopsy was not performed. Continuation of anticoagulation with oral anticoagulants has not been used and although unconventional, has not been associated with any untoward sequelae.

Eight of the 11 patients were treated intravenously with systemic anti-Staphylococci antibiotics for ten to 28 days, until the clinical findings and the blood cultures had become negative and fever had subsided.

One death was directly related to complications of septic thrombophlebitis in a 46-year-old woman (case 4) with Crohn’s disease and rectovaginal fistula. Septic pulmonary emboli with multiple pulmonary abscesses and gangrene of the right leg developed and she subsequently died of septic shock. Death of the other 2 patients was not related to central venous thrombosis. The first one, a 63-year-old woman (case 5), died of chronic congestive failure two weeks after the central venous thrombosis had subsided. Autopsy was not done. The second patient, an 11-year-old white girl who had had a modified Fontan procedure for congenital heart disease, died three weeks after the acute episode of central venous thrombosis. Autopsy showed that the thrombus extended into the right atrium. Seven patients were discharged from the hospital, 5 entirely asymptomatic and the other 2 with mild to moderate edema of the involved extremity.

Discussion

Catheterization of the subclavian vein is a widely accepted technique for the administration of TPN. The incidence of complications related to catheter placement have been described (Table 1). However, thrombosis and septic thrombophlebitis of the subclavian vein and its tributary branches are not frequently clinically recognized or reported and represent late potentially lethal complication. In 1971 Burri and Gasser, in a collective review based on 7225 subclavian catheterizations, noted that clinical signs of central venous thrombosis were reported in 0.7% of cases. In their own prospective study of 1098 catheterizations, they noted a 1.5% incidence. Recently, 34 cases of clinically documented central venous thrombosis in patients receiving intravenous hyperalimentation have been reported, representing a 0.2% to 2.3% incidence. Other authors reported a higher incidence in their series that varied from 4.8% to 10.4% in 104 and 77 patients, respectively. Autopsy incidence of central vein thrombosis in patients who received total parenteral nutrition is even greater, occurring in 6.5% to 21% of patients. Hoshal and Nordlund, also in a postmortem series demonstrated the formation of fibrin sleeves around the catheter in 35% and 100% of 31 and 46 patients, respectively, who had central venous catheters. Axellson in a retrospective phlebographic study of 27 patients receiving TPN, demonstrated that 7 patients with central vein thrombosis were completely asymptomatic. In a similar series, Braun and Teske found a 35% venographic incidence of thrombus formation after seven days of catheter placement. Our own experience with patients having venograms before home parenteral nutrition catheter placement also shows a 20% incidence of subclavian vein thrombosis that is not clinically apparent.

Many factors have been reported to be related to the pathogenesis of catheter-induced central venous thrombosis. Most are associated with endothelial and intimal injury during catheter insertion, particularly when difficult or multiple venipunctures are required, as noted in 5 of our 11 patients. Catheter malposition, reinsertion, manipulation, and a break in sterile technique may play an important role in thrombogenesis. The presence of a foreign body within the vessel lumen induces platelet aggregation and formation of nidus of microthrombus, both at the point of catheter entry, and the level where the catheter tip touches the vessel. The administration of a hypertonic solution in a large caliber vessel has been proved not to be a problem. Sepsis, hypotension, dehydration, and congestive heart failure leading to venous collapse or stasis had also been incriminated. Focal and systemic infectious processes have also been implicated as a cause of central venous thrombosis, particularly in burn patients. In 55% of our patients, 6 of 11, Staphylococcus bacteremia was documented during the initial 24 to 48 hours that preceded the typical physical
finding of central venous thrombosis. A consistent etiologic factor is the presence of a stiff polyethylene catheter with thrombogenic properties as demonstrated by Hoshal et al and Motin et al in the first 24 hours after catheter insertion. Welch et al and Tanzawa et al in experimental and clinical studies, suggested using heparin-coated or silicone catheters to reduce the incidence of this potential complication.

Subclavian vein thrombosis after central catheterization could pass clinically unrecognized as demonstrated in phlebographic and postmortem studies. Once the clinical diagnosis is established and the central catheter is removed, systemic heparinization should be initiated or without a loading dose, which provides an immediate antithrombotic effect, and should be followed by a continuous intravenous administration for ten to 14 days. This technique prevents further proximal propagation of the thrombus, occlusion of the potential collateral circulation, and most importantly, minimizes the risk of pulmonary embolism, which has been estimated to be as high as 12% by Adams et al in patients with primary deep vein thrombosis of the upper extremities. Recently, there have been several reports of pulmonary embolism in patients with central vein thrombosis after subclavian catheterization. Some cases have been fatal. Phlebographic studies after central venous vein thrombosis have demonstrated that the rate of recanalization in the upper extremities is extremely low. Some authors have reported a high incidence of long-term sequelae. However, only 2 of our 7 long-term survival patients had mild persistent edema of the involved extremity, and one had prominent superficial collateral circulation. Because of the potential danger of septic and suppurrative thrombophlebitis, systemic intravenous antibiotic therapy should be administered if sepsis is suspected, and it should be continued if bacteremia or catheter sepsis is documented. Antistaphylococcal antibiotics should be given until culture and sensitivity results are available and antibiotics should then be chosen more specifically.

Suppurative thrombophlebitis of large central veins is uncommon, complicating central venous catheterization. However, if left untreated by aggressive combined intravenous antibiotic therapy and either surgical ligation or excision, the mortality and morbidity is extremely high. Recently, streptokinase has been clinically used successfully in the treatment of central venous thrombosis, particularly in cases in which heparin was not effective.

Subclavian vein catheterization for administration of TPN can be complicated by central venous thrombosis. Prompt recognition and effective therapy can minimize potentially lethal morbidity and reduce the incidence of serious sequelae. Edema, pain, and venous distention in areas close to the insertion or course of a subclavian catheter often associated with sepsis should help to establish the diagnosis. Subclavian venography will confirm the diagnosis. Recommended therapy is catheter removal, heparinization, and antibiotics. Thrombolytic agents may also be of value.

References

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