Catheter-related Thrombosis in Oncologic Patients with Totally Implantable Venous Access Ports in the Forearm

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Purpose

Totally implantable venous access ports (TIVAPs) play an important role in oncologic patients. Forearm ports have shown excellent results regarding technical success, infectious complications and clinical outcome when compared with implantation in the upper arm or pectorally (1, 2). TIVAP placement in the forearm might even be superior to the pectoral approach regarding cosmetic aspects, interference during mammographic imaging and complications during the implantation and explantation procedure (3, 4). However, compared to the pectoral approach one major disadvantage of TIVAP implantation in the forearm position is the significantly higher rate of catheter-related thrombosis (CRT) (5). The role of prophylactic anticoagulation in patients with TIVAPs is a controversial issue, and it is still a matter of debate whether routine thromboembolism prophylaxis is advisable for oncologic patients undergoing implantation of TIVAPs. Furthermore, data on the influence of implantation technique, catheter material, site of implantation, chosen vessel for catheter access and number of vessel punctures during implantation on development of CRT are not sufficiently evaluated for TIVAP implantation in the forearm.

To satisfy the need for more data this study analyses the influence of type and diameter of accessed vein as well as number of vessel punctures and previously administered chemotherapy on the development of CRT in oncologic patients with forearm ports. Furthermore it was evaluated how referring clinicians handle prophylaxis, treatment and follow-up of CRT.
Methods and Materials

Patients

We retrospectively reviewed the archives of our interventional radiology department between March 2010 and November 2010 to identify 200 consecutive patients (94 men, 106 women; mean age 57.7 +/- 14 years) who had undergone implantation of a TIVAP in the forearm. The most common malignancies in our patients were Non-hodgkin lymphoma (n=55, 27.5%), gastrointestinal tumour (n=31, 15.5.%), plasmocytoma (n=28, 14.0%) and gynecological tumour (n=26, 13.0%).

Indications for TIVAP placement were underlying malignancy with the need for artificial nutrition (n=6), administration of chemotherapy and frequent blood sampling (n=194).

Follow-up, data evaluation and endpoint definition

Mean follow-up was 195 days. During follow-up 12/200 patients (6.0%) died.

Medical records were screened to identify patients with CRT and pulmonary embolism (PE). Two authors reviewed angiographic records as well as sonograms and angiograms if existent. Primary endpoint was CRT related to side, type and diameter of the accessed vein as well as the number of punctures of the target vessel during implantation procedure and the number of other veins punctured prior to successfully entering the target vessel.

Catheter-related thrombosis (CRT) was defined as a lack of compressibility, of flow in colour-coded Duplex sonography (Figure 1A, B), or of contrast within the catheter-containing vessel during fluoroscopy (Figure 1C, D) in patients with a swollen and/or painful upper extremity, or congestion of collateral veins on the side of port implantation.
Fig. 1: Axial (A) and longitudinal (B) view of a colour-coded Doppler ultrasound of the left subclavian vein in a patient with suspected catheter-related thrombosis. The port catheter (A, white arrows) is clearly seen within the vessel lumen and seems to be wall-adherent in the axial view. Note the missing flow signal within the vein which is accompanied by a small collateral (B, curved arrow) in the longitudinal view. Again, the port catheter is clearly depicted (B, asterisk). Subtracted (C) and unsubtracted (D) digital subtraction angiography in a patient with suspected CRT and contrast injection via a peripheral vein of the left hand. The port catheter (asterisk) can be seen without contrast filling of the accessed vein, clearly depicting CRT.


Secondary endpoints were impact of prescribed thrombo-embolic prophylaxis by referring physicians after implantation as well as history on thrombosis, coagulation disorder, PE (thrombo-embolic events) and administered chemotherapy prior to implantation. In patients with CRT location of the catheter tip was evaluated using computed tomography studies of the chest or chest x-rays. Extension of CRT was defined as being peripherally (including upper arm and axillary vein) and/or centrally (including subclavian vein and superior vena cava) located. Clinical improvement of symptoms was
defined as complete resolution of pain or arm-swelling. Furthermore attention was given to the aspect of how CRT was treated and whether patients with CRT suffered from clinically relevant pulmonary embolism (PE).

**Statistical analysis**

Statistical analysis was performed using a specialized computer algorithm (SPSS, Chicago, IL, USA). Statistical significance was set at a P value of less than 0.05. For comparison of groups within this study sample the nonparametric two-sample Mann-Whitney-Test and Kruskal-Wallis-H-Test were used. To analyze the influence of multiple punctures of the finally accessed vein, two groups were formed: those with one and those with multiple target vessel punctures.
Results

Altogether 38941 catheter days were analyzed. Catheter-related thrombosis was diagnosed in 21/200 (10.5%) patients, accounting for 0.05/100 catheter days. CRT was diagnosed as early complication in 12/200 patients (6.0%), while in 9/200 (4.5%) CRT was graded as late complication. Mean time to diagnosis of CRT was 45.5 days (range, 4-191d). History of thrombosis, pulmonary embolism and coagulation disorders in the study sample are highlighted in Table 1. We found no effect of thrombo-embolic history on development of CRT (p>0.05, Mann-Whitney-Test).

Table 1. History of thrombo-embolic incidents and coagulation disorder up to the time of TIVAP implantation

<table>
<thead>
<tr>
<th></th>
<th>Number (n=32)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep vein thrombosis</td>
<td>22</td>
<td>11.0%</td>
</tr>
<tr>
<td>(DVT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2</td>
<td>1.0%</td>
</tr>
<tr>
<td>(PE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT and PE</td>
<td>6</td>
<td>3.0%</td>
</tr>
<tr>
<td>Coagulation disorder*</td>
<td>2</td>
<td>1.0%</td>
</tr>
<tr>
<td>* Heparin-induced thrombocytopenia (HIT) and lack of factor VIII</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In forty-five patients (22.5%) vascular access was established in the right, in 155 patients (77.5%) in the left forearm (p=0.001, Chi-square test). We found significantly more patients with CRT in the group with port implantation in the left forearm (p=0.04, Mann-Whitney-Test) (Table 2).

Table 2. Relation of CRT to device type, side of implantation and number of vessel punctures

<table>
<thead>
<tr>
<th></th>
<th>Number (n=200)</th>
<th>Percentage</th>
<th>Number of CRT (n=21)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-Port®</td>
<td>70</td>
<td>35%</td>
<td>5</td>
<td>p=0.26</td>
</tr>
<tr>
<td>P.A.S. Power®</td>
<td>130</td>
<td>65%</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Left forearm</td>
<td>155</td>
<td>77.5%</td>
<td>20</td>
<td>p=0.04</td>
</tr>
<tr>
<td>Right forearm</td>
<td>45</td>
<td>22.5%</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Puncture Type</td>
<td>Count</td>
<td>Frequency</td>
<td>CRT Patients</td>
<td>p-value</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------</td>
<td>-----------</td>
<td>--------------</td>
<td>---------</td>
</tr>
<tr>
<td>One puncture</td>
<td>173</td>
<td>86.5%</td>
<td>20</td>
<td>0.22</td>
</tr>
<tr>
<td>Multiple punctures</td>
<td>27</td>
<td>13.5%</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

In 12/21 patients (57.1%) CRT extended into centrally located veins. During follow-up 12/21 patients (57.1%) with CRT showed clinical improvement of CRT-related symptoms. Thrombus formation on the catheter tip was detected in 6/200 (3.0%, 0.015/100 catheter days), formation of a fibrin sheath was seen in 1/200 patients (0.5%) (Figure 2).

![Fig. 2](image-url): Subtracted (A) and unsubtracted (B) digital subtraction angiography after contrast injection via the TIVAP. Note the small filling defect (curved arrow) indicating thrombus formation on the catheter tip which is located below the carinal level. Another TIVAP (C) with careful contrast injection via the device in which injection was possible while aspiration was not: atypical contrast media exit at the catheter tip with backflow (black arrow) along the catheter extending into the brachiocephalic vein, suggestive of fibrin sheath formation. After a second more forceful injection the fibrin sheath ruptured (black arrow) on the left side at the height of the carina with contrast distribution in the superior vena cava.

In 19/21 patients (90.5%) with CRT the tip of the catheter was positioned below the carina, while in two patients the tip was localized within 2cm cranial to the carina but within the superior vena cava. Mean diameter of the accessed vessels was 3.6 +/- 1.4 mm. Details on type, diameter and CRT of the accessed veins are given in Table 3. There was no statistically significant difference in catheter-related thrombosis between vascular access via basilic, brachial and cephalic vein (p>0.05, Kruskal-Wallis-H-Test).

Table 3. Summary of accessed vessel, mean diameter and number of CRT

<table>
<thead>
<tr>
<th>Accessed vessel</th>
<th>Number (n = 200)</th>
<th>Mean and standard deviation</th>
<th>Catheter-related thrombosis (n = 21 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basilic vein</td>
<td>150 (75.0%)</td>
<td>3.7 +/- 1.3 mm</td>
<td>13</td>
</tr>
<tr>
<td>Brachial vein</td>
<td>39 (19.5%)</td>
<td>3.5 +/- 1.1 mm</td>
<td>8</td>
</tr>
<tr>
<td>Cephalic vein</td>
<td>11 (5.5%)</td>
<td>3.5 +/- 2.0 mm</td>
<td>0</td>
</tr>
</tbody>
</table>

The finally accessed vein for TIVAP implantation was once (n=173), twice (n=19), three- (n=5) or four times (n=3) punctured to succeed in placement of the peel-away sheath. The number of attempts had no influence on the onset of CRT (p>0.05, Mann-Whitney-Test). In 44/200 patients (22.0%) one (n=28) or two (n=16) veins apart from the finally accessed vessel had been unsuccessfully punctured before vascular access was finally gained. Unsuccessful puncture of a different vein other than the finally accessed one had no influence on CRT development (p>0.05, Mann-Whitney-Test). Ninety-five patients (47.5%) had been administered chemotherapy prior to TIVAP implantation. A history of administered chemotherapy had no significant influence on formation of CRT (p>0.05, Mann-Whitney-Test). Although no recommendation was given in our interventional radiology report on the implantation procedure, referring physicians put 94/200 patients (47.0%) on weight adapted low molecular weight heparin (LMWH) for thrombo-embolic prophylaxis. In addition, six patients were already on prophylactic anticoagulation with LMWH (n=5) or warfarin (n=1) due to history of a thrombo-embolic event. There was no statistically significant difference (p>0.05, Mann-Whitney-Test) in CRT rates between patients who received such prophylaxis and those who did not. After CRT had been diagnosed no patient developed clinically relevant pulmonary embolism. All devices remained functional and were utilized after CRT had been diagnosed.
Conclusion

Recent experience with forearm ports has shown a remarkably higher rate of catheter-related thrombosis when compared to pectorally-placed devices (1, 2). Probable explanations for this circumstance include a longer way of the port catheter within smaller-sized vessels and higher mechanical stress during arm movements. There are potential advantages of TIVAP placement in the forearm, e.g. better cosmetic results, no risk of pneumothorax during implantation, no interference of the device with mammographic or chest imaging (3); therefore we conducted this study to identify further risk factors, e.g. target vessel type or size and history of thrombo-embolic events, that might induce CRT, so that in patients with an increased risk for CRT and planned TIVAP placement in the forearm alternative implantation sites (e.g. pectoral) could be chosen.

We detected CRT in 10.5% of patients with a forearm port. This rate is higher than in pectorally-placed devices and similar to data of other studies on upper- or forearm ports: one study found CRT in 4.8% of chest and 11.4% of arm ports (5). This has been explained by smaller diameters of accessed vessels for arm port placement and by arm movements, increased kinking of the catheter, mechanical displacement of the catheter, or a knot in the catheter at the level of the armpit, although one should differentiate between upper- and forearm placement when discussing mechanical stress on TIVAPs (5-7). These factors may be responsible for changes in blood flow or might injure the vascular endothelium and thus trigger clot formation (6). Another risk factor for CRT not covered by our data is represented by catheter tip dislocation above the carinal level; this complication has been described after forearm as well as chest port implantation (Figure 3).
**Fig. 3:** Unsubtracted (A) and subtracted (B) DSA images following contrast injection via an antecubital vein in a patient 3 months following chest port implantation. Note the dislocated catheter tip which is located above the carina (asterisk) and the filling defect (circle) of the left cephalic, subclavian and brachiocephalic vein, depicting catheter-associated thrombosis.

**References:** Radiology, Zentrum Operative Medizin, Universitätsklinikum Würzburg - Würzburg/DE

So far we have not found any data on the aspect of which vessel should be accessed for port placement in the forearm to decrease the risk of CRT. Similar to Lenhart et al. (8) the by far most often accessed vessel in our study was the basilic vein, probably because it is the largest vein in the majority of our patients. Our data suggest that the type of vein chosen for vascular access in the upper arm has no influence on the development of CRT. Although vessel diameters showed no statistically significant difference in patients with and without CRT we suggest sonographic identification of the largest vein of the upper arm, which can then be accessed under sonographic guidance. Larger diameters might be easier to puncture than smaller ones, thus contributing to patient comfort and decreasing the overall time for implantation. As DVT needs to be ruled out prior to implantation anyway, this procedure does not significantly increase overall procedure time. As opposed to fluoroscopic-guided vascular access this method does not expose
patients to any radiation and we believe this method to be more adequate for defining the largest vein, as sonographic evaluation offers an axial view.

In some patients multiple punctures of the target vein may be necessary to gain vascular access. Our data suggest that multiple punctures of the target vessel or unsuccessful puncture of another vein in the same arm has no influence on development of CRT and can therefore be performed without increased risk of the latter.

Our data suggest that TIVAP placement on the left side is associated with a higher risk for CRT. Although existing literature on TIVAPs in the forearm has failed to identify (9), let alone evaluate differences in occurrence of CRT regarding left- or right-sided placement (10, 11), our results correlate well with already published studies on upper arm and chest port implantation regarding an increased risk for CRT following implantation on the left side (4, 12). It is hypothesized that the angle between left innominate vein and superior vena cava accounts for an increased risk of vascular wall damage with subsequent increased risk for CRT. This aspect may be important, as the majority of our patients is right-handed and we regularly implant TIVAPs in the non-dominant left arm to minimize effects on the quality of life.

The role of thrombo-embolic prophylaxis has been discussed controversially and literature on using either warfarin or LMWH is inconsistent (4). Nevertheless guidelines have been implemented that clearly state that no anticoagulant drugs should be given for primary prevention of CRT in oncologic patients (13). In this context the high percentage (almost half of our patients received TEP from their referring physician) of patients who received LMWH was a surprising fact and in the future we will mention in our interventional procedure report that no prophylactic anticoagulation is recommended after TIVAP implantation in the forearm, not only because this unnecessarily increases costs but maybe also the rate of bleeding complication. Another study supports this strategy as the authors found that TEP with LMWH was only partly effective after chest-but not after arm port placement (6).

Treatment of CRT with therapeutic doses of LMWH was clinically effective in only about half of the affected patients, although suggested as the treatment of choice by recent guidelines (13). Another study analyzed the resolution of catheter-associated upper extremity venous thrombosis and also found a high rate of persisting CRT despite therapeutic anticoagulation with LMWH, although it included only a small number of patients with peripherally-placed TIVAPs (14). The authors concluded that removal of central venous access alone would improve resolution of CRT. In accordance with these authors and current guidelines we recommend anticoagulation with therapeutic doses of LMWH and further utilization of the port as long as it is needed (13, 14), of course depending on the severity of symptoms.

There are three main limitations to this study. First, this series is retrospective and lacks randomization. Therefore, patient selection bias may be present in our results. A prospective study including repeated colour-coded Doppler sonography or phlebography...
examinations would be necessary to define the exact prevalence of CRT. Second, only a prospective and randomized trial with patients having chest and forearm ports could define efficacy of thrombo-embolic prophylaxis. Third, a further selection bias may have influenced the results with regard to the side of implantation, as in most patients the non-leading arm was preferred.

CONCLUSION

TIVAPs in the forearm have a certain risk of early and late phase CRT. Regarding CRT development it does not matter whether the catheter is inserted via the basilic, brachial or cephalic vein. Therefore, for easiest access, the largest vein should be chosen after having been identified with ultrasound. CRT prophylaxis with low molecular weight heparin seems to be rather ineffective in patients with TIVAPs implanted in the forearm.
References


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