

CHAPTER IV

**COMPLICATIONS OF VENOUS ACCESS PORTS IN 132 PATIENTS  
WITH DISSEMINATED TESTICULAR CANCER  
TREATED WITH POLYCHEMOTHERAPY**

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## ABSTRACT

*Venous access ports (VAPs) can be used to administer polychemotherapy to patients with malignancies. The purpose of this study was to evaluate perioperative and late complications related to VAP implantations and to analyse factors that may predict the development of complications. During the period 1983 to 1994, 135 VAPs were implanted in 132 patients with disseminated testicular tumors. In a retrospective study, the perioperative and late complications were recorded in this homogeneous patient group. Multivariate analysis was performed to detect factors that may predict the development of complications. The median age of the patients was 28 (range 16-55) years. Perioperative complications were recorded in five patients (3.7%): pneumothorax in two (1.5%), blood loss in two (1.5%) and mediastinal bleeding in one (0.7%). The ports remained in situ for a total of 55247 days, median 413 (range 7-1607) days. In 31 patients (23%), 42 late complications developed (31%): system obstruction in 13 (9.6%), thrombosis in 11 (8.1%), infection in six (4.4%), catheter defect in six (4.4%), extravasation in four (3.0%) and local skin necrosis in two (1.5%). Late complications were significantly more common in the patients who had received chemotherapy prior to VAP implantation ( $P < .001$ ). Univariate analysis showed that there were significantly more complications after VAP implantation under local anesthesia than under general anesthesia ( $P < .05$ ). Polychemotherapy could be administered in an adequate manner using a VAP. Complications occurred in 26.7% of a homogeneous group of patients who received a VAP implantation for polychemotherapy for disseminated testicular cancer. Chemotherapy treatment prior to VAP implantation was the only independent risk factor for late complications.*

## INTRODUCTION

At the end of the 1970s, cisplatin became available for use in polychemotherapy combinations to treat patients with disseminated testicular cancer. This considerably improved the prognosis of these patients.<sup>1</sup> In the most frequently used chemotherapy combinations, PVB (Platinum, Vinblastine and Bleomycin)<sup>1</sup> and BEP (Bleomycin, Etoposide and Platinum),<sup>2</sup> cisplatin is administered for five

consecutive days. To prevent nephrotoxicity induction by cisplatin, it is necessary to perform pre- and post-hydration. In addition, blood samples have to be obtained frequently to monitor the efficacy and toxicity of the polychemotherapy. Vena puncture and long-term peripheral infusions may damage the venous intima. Sclerosing effects of cytostatics often cause chemical thrombophlebitis, while intima damage and thrombophlebitis lead to secondary thrombosis.<sup>3</sup> Consequently, it is more difficult to insert a peripheral infusion and the risk of extravasation increases.<sup>4</sup>

Since the introduction of chemotherapy, a great deal of attention has been paid to achieve an adequate means of venous access that is suitable for long-term use.<sup>5</sup> Based on the poor experience with peripheral access infusions, at the University Hospital Groningen, the Netherlands, initially arteriovenous (AV) shunts were used for this purpose. Although these shunts were used widely for haemodialysis, they proved to be unsuitable for the long-term administration of chemotherapy to patients with disseminated testicular tumors. Even though this is a young otherwise healthy patient population a high incidence of phlebosclerosis and thrombosis was noted.<sup>3</sup> In 1982, the venous access port (VAP) was introduced for administering chemotherapy. A reservoir was implanted subcutaneously and attached to a catheter that provided access to the central blood vessels.<sup>6</sup> This system, which was fully implanted under the skin, carried a low risk of infection and imposed little or no restriction to the patient in the daily activities.<sup>6-8</sup> Because of the disappointing experiences with peripheral access infusions and AV shunts, at the University Hospital Groningen, from 1983 the VAP was used for the administration of cisplatin-based polychemotherapy to patients with disseminated testicular cancer.<sup>9</sup> This report describes more than ten years of experience with the VAP in this homogeneous patient group. The occurrence of perioperative and late complications related to the VAP were studied and special attention was paid to factors that may predict the development of late complications.

## PATIENTS AND METHODS

In the period from January 1983 to January 1994, 135 VAPs (Strato/Infusaid Inc. Norwood, MA, USA) were implanted in 132 patients with disseminated testicular cancer at the University Hospital Groningen. The VAPs consisted of a

polysulphonate port with a 8 french radiopaque silicon catheter I.D. 1.0 mm x O.D. 2.5 mm. Clinical staging was conducted according to Peckham et al.<sup>10</sup> The tumors were classified according to the nomenclature of the World Health Organisation.<sup>11</sup> In principle, the VAP was implanted before polychemotherapy treatment was started. Prior to 1989, patients with a disseminated testicular tumor underwent a staging laparotomy to determine the extent of retroperitoneal metastases.<sup>12</sup> During the operation, the VAP was also implanted. Nowadays clinical staging is performed with CT scanning of the abdomen and thorax and the VAP is implanted exclusively under local anesthesia.

The heparin-filled VAP was inserted into a small subcutaneous pocket via a transverse skin incision 8 cm above the left areola mamma. The port was not secured in the pocket. Subsequently, a catheter was introduced into the left subclavian vein according to the Seldinger technique. The position of the tip of the catheter was monitored with X-ray screening. At this stage, the patency of the VAP was also checked. After implantation, a chest X-ray was taken to exclude a pneumothorax and determine the exact position of the catheter. If it was not possible to apply the Seldinger technique for technical reasons, venotomy of the cephalic vein or external jugular vein was performed and catheter-placement followed.

The use of the VAP was standardized according to protocol. Before starting chemotherapy, the intravascular position of the catheter was verified by taking a blood sample via the VAP. If it was not possible to obtain a blood sample, magnesium sulphate was injected into the port to exclude extravasation or thrombosis.<sup>13</sup> At the start of a treatment cycle, the port was punctured once only with an L-shaped Huber point needle (B. Braun Medical BV, Melsungen, Germany) and the area was covered with a sterile dressing until the total infusion process was completed. After completion of the treatment cycle, the system was flushed with saline solution and filled with heparin. The VAP remained in situ for up to one year after polychemotherapy had been completed. If there was no tumor recurrence in this period, the VAP was removed.

Perioperative and late complication of the VAP were evaluated in retrospect. The following peroperative complications were studied: pneumothorax, excessive blood loss during puncture of the subclavian vein, mediastinal haematoma and damage to adjacent nerves.<sup>14-17</sup> The following late complications were studied:

thrombosis, local and systemic infection, system obstruction, extravasation, local skin necrosis and catheter defects, i.e. fracture and rupture.<sup>15,18-20</sup> Table 1 presents an overview of the definitions used for these late complications.

**Table 1. Definitions**

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**Thrombosis**

Thrombosis of the subclavian vein and/or axillary vein\*

**Infection**

- *Local*: erythema of the skin and pain at the port site, with or without bacteriological confirmation
- *Systemic*: fever, with or without bacteriological confirmation, which disappeared after the catheter had been removed

**System obstruction**

Obstruction in the reservoir and/or catheter, without thrombosis

**Extravasation**

Escape of cytostatics from the blood vessels

**Local skin necrosis**

Necrosis of the skin at the port site, with or without perforation

**Catheter defect**

- *Catheter fracture*: a segment of the catheter-part of the VAP broke off
  - *Catheter rupture*: leakage of cytostatics through a rupture in the catheter-part
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\* Diagnosed clinically and confirmed with Doppler

Late complications were evaluated in relation to the following *patient* characteristics: age, clinical stage of the testicular tumor, histology of the primary tumor, chemotherapy prior to implantation, increased tumor markers AFP and/or hCG before treatment, bone marrow depression during chemotherapy and a history of thrombosis. Late complications were also evaluated in relation to the following *VAP* characteristics: implantation side, the vein that was used, the position of the catheter tip, the number of attempts to implant the VAP, complications during implantation of the VAP, local anesthesia versus general anesthesia and the operator; surgeon versus surgical resident. The number of complications is expressed per 1000 patient days, i.e. the number of

days that the VAP was in situ.<sup>21</sup> Follow-up continued until the VAP was removed or the patient died.

### **Statistical analysis**

Differences in patient characteristics and VAP characteristics between the two subgroups of patients with and without complications were analysed as continuous variables by means of Student's *t* test (all complication together) or the Mann-Whitney test (each complication separately). The Chi-square test was used for categorical variables and Fisher's exact test for small numbers. Multivariate logistic regression analysis was performed to evaluate independent associations between the various prognostic factors and the occurrence of complications. Possible prognostic factors were chosen on a theoretical basis and on the basis of the univariate analyses.<sup>22</sup> The following prognostic factors were included in the multivariate analyses: age, clinical stage IV (yes versus no), pre-VAP chemotherapy (yes versus no), number of implantation attempts (>1 versus 1) and the type of anesthesia (local versus general). The presence of a late complication was the dependent variable with the absence of a complication as reference category. In the multivariate analyses, patients with multiple complications were considered as separate cases for each complication. The level of statistical significance was set at  $P < .05$ . Odds ratios were considered to be significant if the 95% confidence interval did not contain the value 1. Statistical analyses were conducted using the SPSS-PC+ statistical software package (SPSS Inc. Chicago, Ill., USA).

## **RESULTS**

A total of 135 VAPs were implanted in 132 patients who underwent cisplatin-based chemotherapy for disseminated testicular cancer. The median age was 28 (range 16-55 years, SD 7.8) years. In 125 patients the primary tumor was a nonseminomatous testicular tumor (94.7%); the seven remaining patients had a seminoma (5.3%). At the time of VAP implantation, 59 patients had stage II disease (44.7%), 14 had stage III (10.6%) and 58 had stage IV (43.9%). In one patient the stage was unknown (0.8%). It was necessary to start chemotherapy

immediately in 13 patients (9.8%) due to poor clinical condition and/or extensive metastatic disease. In these 13 cases, the VAP was implanted at the first opportunity, usually directly after the first treatment cycle. The median number of polychemotherapy cycles was four (range 1-14).

The techniques used to implant the 135 VAPs were the Seldinger method, i.e. subclavian vein puncture (n=126, 93.3%), venotomy of the cephalic vein (n=8, 5.9%) and venotomy of the right jugular vein (n=1, 0.8%). Implantation was conducted under general anesthesia during a staging laparotomy<sup>12</sup> in 103 cases (76.3%) and under local anesthesia in 32 cases (23.7%); 121 VAPs were implanted on the left and 14 on the right (10.4%). In 19 patients, more than one attempt was made to position the catheter correctly. The tip of the catheter was located in the superior vena cava in 126 cases (93.3%), in the right atrium in five cases (3.7%) and in the internal jugular vein in four cases (3.0%).

### **Perioperative complications**

Perioperative complications occurred in five of the 135 VAPs (3.7%). These comprised a pneumothorax in two patients (1.5%) which necessitated thorax drainage; excessive blood loss in two patients (1.5%) which could be treated conservatively and mediastinal bleeding in one patient (0.8%) in whom the VAP implantation procedure had to be discontinued.

### **Late complications**

The 135 VAPs were in situ for a total of 55247 days and there were 42 (31.1%) complications in 31 patients. Eight patients had two complications and one patient had four complications. The total number of complications corresponds with 0.76 complication episodes per 1000 patient days. The median implantation time of the VAPs was 413 (range 7-1607) days. In four VAPs, all without complications, the precise number of days in situ was unknown. The incidence of late complications was therefore calculated for 131 VAPs. In the subgroup of VAPs with one complication, the median number of days in situ was 308 (range 55-1055) days, while in the subgroup with more than one complication, it was 265 (range 78-894) days. There were no complications in 101 patients (76.5%). During follow-up, 13 patients died (10.2%); mortality was not related to VAP

complications. Table 2 lists the late complications.

**Table 2. Incidence and interval until late complications occurred in 135 VAPs**

Complication	No. of patients	Incidence <sup>1</sup>	No. of days (range) <sup>2</sup>
System obstruction	13 (9.6%)	0.24	40 (5-601)
Thrombosis	11 (8.1%)	0.20	33 (2-518)
Infection	6 (4.4%)	0.11	75 (39-430)
Extravasation	4 (3.0%)	0.06	72 (41-85)
Local skin necrosis	2 (1.5%)	0.04	197 (60-333)
Catheter defect	6 (4.4%)	0.11	363 (55-1241)

<sup>1</sup> Per 1000 patient days; <sup>2</sup> Median number of days in situ until complication occurred.

*System obstruction* was the most frequent complication. The obstruction could be alleviated by injecting the VAP with saline solution, heparin or urokinase.

*Thrombosis* was diagnosed clinically (redness, swelling and pain) and was confirmed with Doppler scanning. It occurred in 11 cases: six in the subclavian vein, four in the axillary vein and in one in the brachiocephalic vein. The port was removed for this reason in one patient, four patients received a thrombolytic agent and six patients were treated expectatively. All patients recovered fully from this thrombosis, which was confirmed with Doppler scanning.

*Infection*: six cases of infection occurred in five patients. Infection was local in two patients. There were four cases of systemic infection in three patients. All these patients received intravenously antibiotic therapy. Two of the three VAPs had to be removed because of continued systemic infection.

*Extravasation* occurred in four patients and comprised subcutaneous leakage of the cytostatics at the port site. Three of these patients were treated conservatively; the VAP was removed in one patient.

*Local skin necrosis* developed in two patients at the port site. In both cases, the VAP had to be removed.

*Catheter defects*: these mechanical complications occurred in six cases (five

fractures and one rupture). Two of the five fractures were detected on routine chest X-ray 256 and 454 days after implantation, respectively. The remaining three fractures were detected during VAP removal after 350, 376 and 1241 days, respectively. The broken catheter segments migrated to the pulmonary artery in four of the five cases and to the right atrium in the remaining patient. In all cases they could be removed by catheterisation under local anesthesia via the femoral vein.<sup>19</sup> The catheter ruptured in one patient after 55 days, replacement of the VAP was performed.

The relationship between patient characteristics and late complications was analysed. Of the 13 patients who had received chemotherapy prior to VAP implantation, 9 (69.2%) developed at least one late complication. This was significantly different from the 33 complications (27.7%) that occurred in the 119 patients who started chemotherapy after VAP implantation ( $P < .001$ ). The difference was mainly due to thrombosis ( $n=4$ ) and system obstruction ( $n=4$ ) in the pre-chemotherapy implantation group versus seven thromboses and nine system obstructions in the post-chemotherapy implantation group ( $P < .05$ ). No significant relationships were found between late complications and: age, clinical stage, histology of the primary tumor, increased tumor markers, bone marrow depression and a history of thrombosis (data not shown).

Analysis was also made of the relationship between the implantation procedure of the VAP and late complications. In the 32 VAPs that were implanted under local anesthesia, 12 patients had one or more late complications (37.5%). This differed significantly from the 19 (18.4%) complications that occurred in the 103 implanted VAPs under general anesthesia ( $P < .05$ ). This difference was mainly due to thrombosis: four cases in the 32 VAP implants conducted under local anesthesia versus seven cases in the 103 implants conducted under general anesthesia. No significant relationships were found between late complications and: implantation side, implantation vein, position of the catheter tip, number of attempts to position the catheter, complications during implantation and the operator (data not shown).

Multiple logistic regression analysis was performed to examine the relationship between each patient characteristic or VAP characteristic and the occurrence of late complications, adjusted for the remaining potential characteristics (Table 3). Chemotherapy treatment prior to VAP implantation was found to be the only independent risk factor for late complications (Odds Ratio 7.4; 95% Confidence Interval 1.8-30.4).

**Table 3. Multiple logistic regression analysis: Odds Ratios for the occurrence of late complications (n=135)\***

Independent variable	Odds Ratio	95% CI
Age	1.0	0.9 - 1.1
Stage IV (yes versus no)	1.2	0.5 - 2.9
Pre-VAP chemotherapy (yes versus no)	7.4	1.8 - 30.4
Number of attempts (>1 versus 1)	2.1	0.7 - 6.4
Anesthesia (local versus general)	1.5	0.5 - 4.5

\* No complication was the reference category

## DISCUSSION

Aubaniac was the first to describe the use of a central catheter in 1952.<sup>23</sup> It was mainly used for parenteral feeding.<sup>24</sup> In 1973, Broviac introduced the tunneled silicone rubber catheter,<sup>25</sup> which was adapted later by Hickman and Ivey.<sup>26,27</sup> These central venous catheters carried the disadvantages of an increased risk of infection and inconvenience for the patient.<sup>28-30</sup> Since the introduction of the VAP in the eighties, various authors have evaluated its advantages over traditional external catheters.<sup>7,31</sup> In a prospective randomized study, Mueller et al. did not find any significant difference in the incidence of infection, thrombosis or mechanical complications between the VAP and the external catheter.<sup>31</sup> Carde also performed a prospective randomized study and found that in patients with a solid tumor who had been receiving treatment with intravenous chemotherapy for longer than six months, the totally implantable systems were more reliable, safer and better tolerated than the traditional external catheters.<sup>7</sup> The totally implantable systems are cosmetically superior and more easily accepted by the patients than the external catheters.<sup>6</sup> Therefore, the VAP usually takes preference as access system for chemotherapy.

This is the first study to describe the use of the VAP on a large homogeneous patient group and to use it exclusively for administering cisplatin-based

chemotherapy. Other authors described complications that occurred with the VAP in patients with diverse malignancies and non-malignancies.<sup>15,18,32,33</sup> In a great number of these studies, the VAP was not only used for administering chemotherapy, but also for other purposes, such as parenteral feeding and/or blood transfusions.

In this study, two types of complications were distinguished: perioperative and late complications. The number of complications in this homogeneous patient group did not differ essentially from the percentages reported in the literature for various patient groups. The number of perioperative complications consisting of pneumothorax and blood loss was described in percentages of 1.7 to 8.0%.<sup>14,15,34,35</sup> Late complications consisting of system obstruction, thrombosis, infections, extravasation and local skin necrosis was described in percentages of 0.0 to 55.5%.<sup>14,15,21,31-43</sup> Only the percentage of catheter defects (4.4%) was larger than in the other studies (0.4%-1.4%).<sup>31,32,33,39</sup> Possible explanations for this are: too medial positioning which caused friction of the catheter between the clavicle and the first rib ('pinch off sign') and/or the long duration in situ time.<sup>44,45</sup>

The incidence of complications per 1000 patient days was also in agreement with the incidences reported in other studies (Table 4). The VAPs in this study remained in situ for much longer than they did in other studies and were consequently at risk for a longer period, because at the University Hospital Groningen, it was decided to leave the VAPs in situ for up to one year after the completion of treatment so that if recurrent disease was diagnosed, chemotherapy treatment could be continued via the VAP. However, leaving the VAP in situ for a longer period increased the risk of catheter defects. Therefore, it may be worth considering earlier removal.

In 13 patients, chemotherapy had to be started immediately because of extensive metastatic disease and/or poor clinical condition. Both univariate and multivariate analyses showed that a significantly greater proportion of these patients developed late complications ( $P < .001$ ; Odds Ratio 7.4). These were mainly venous thrombosis and system obstruction. Donohue and Rowland reported that morbidity, unfortunately not further specified, was higher in the patients who underwent laparotomy after chemotherapy for a testicular tumor, than in those who had not received chemotherapy.<sup>46</sup> Their explanation was that the ensuing decrease in pulmonary, renal and nutritive reserves may have caused this increase in morbidity.

**Table 4. Complication incidence expressed as the number of episodes per 1000 patient days**

	Lokich'85 <sup>36</sup>	Brothers'88 <sup>15</sup>	Freytes'90 <sup>18</sup>	Grannan'90 <sup>14</sup>	Ramirez'93 <sup>32</sup>	Lemmers'96
<b>Patients</b>						
number	92	300	128	66	176	132
age range	n.d.	9-83	18-82	22-82	16-76	16-55
<b>VAPs</b>						
number	92	329	134	66	185	135
application	A	B	A	B	A	C
days in situ						
- median	127	257	308	152	276	413
- total	12797	116208	40628	10016	51150	55247
<b>Complication ratio's</b>						
thrombosis	1.20	0.13	0.02	0.20	0.10	0.20
infection	0.63	0.46	0.07	0.39	0.08	0.11
system obstr.	1.02	0.26	0.07	n.d.	0.10	0.24
extravasation	0.47	0.18	0.05	n.d.	0.14	0.06
skin necrosis	n.d.	0.04	0.05	n.d.	n.d.	0.04
catheter defect	n.d.	n.d.	n.d.	n.d.	0.04	0.11
total	3.32	1.07	0.26	0.59	0.46	0.76

Abbreviations: A, administration of various chemotherapy combinations to patients with various types of malignancy; B, A plus administration of parenteral feeding and blood products to patients with various types of malignancy and non-malignancy; C, administration of cisplatin-based polychemotherapy to patients with testicular cancer; n.d., not described.

The patients who had received chemotherapy before VAP implantation showed a greater number of complications, although this pre-VAP chemotherapy was administered by peripheral access infusions. This may be due to the sclerosing effects of cytostatics. Univariate analysis showed that there were significantly more complications in the VAPs that had been implanted under local anesthesia

than under general anesthesia ( $P < .05$ ); these were also mainly thrombosis. A possible explanation for this is that it was easier to puncture the subclavian vein under general anaesthesia with positive pressure mechanical ventilation causing vasodilatation, than under local anesthesia. However, this did not prove to be an independent risk factor in the multivariate analysis.

Mansfield found a lower percentage of complications in catheterisations of the subclavian vein performed by experienced physicians (10.2%) than in those performed by inexperienced physicians (13.5%); however, this difference was not statistically significant.<sup>35</sup> In this study, the number of complications was not related to the experience, surgeon versus surgical resident.

In conclusion, implantation and use of a VAP to administer polychemotherapy to patients with disseminated testicular cancer was accompanied by a complication rate of 26.7%. The only independent risk factor for occurrence of late complications in this study was the administration of chemotherapy prior to VAP implantation. Therefore, in patients with a diagnosis of disseminated testicular cancer who are scheduled to undergo long-term polychemotherapy, the VAP must be implanted before chemotherapy treatment is initiated.

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