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Tissue reaction induced by implanted venous access ports in adult patients after infection of the implantation site

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Abstract. Implantable long-term central venous port systems (CVPS) are widely used as a permanent means of accessing the vascular system for intravenous delivery of drugs, parenteral nutrition, blood transfusion, and blood sampling. These systems allow easy and repetitive puncture without causing much damage to the vessels. However, the body foreign surface of CVPS induces an inflammatory response with varying intensity (depending on the implant materials) that leads to formation of a fibrous tissue capsule around the implant. This study was designed to investigate the influence of bacterial infection on the tissue reaction induced by implanted CVPS in adult patients. 20 patients (9 women, 11 men, 58 ± 14 yrs of age) were included in this study. These patients received explantation of a polysulfone based CVPS (ChemoSite™, Covidien, Mansfield, USA) due to port related infections (patients with bacterial infections at the implantation site: group A, 5 men, 1 women) or to other reasons such as termination of treatment, thrombosis, or CVPS dysfunction (patients without bacterial infections, group B, 6 men, 8 women) 299.9 ± 261.2 days after CVPS implantation. A sample of the encapsulating tissue covering the CVPS together with surrounding tissue (at least 1×1 cm^2) was placed in a small container with fixing agent, a buffered neutral 4% formalin solution (pH 7). Histological sections of the samples were prepared for light microscopic analysis after paraffin embedding. Sections of 3 μm were cut and stained with haematoxylin and eosin, Weigert´s elastic stain, and Heidenhain's azan stain. There was no difference in thickness, collagen and elastin content, or cell and capillary density of the fibrous capsule between both groups. Due to the wound healing reaction involving angiogenesis and fibroblast activation cell density and number of capillaries in the capsule tissue of all patients showed a positive correlation ($r = 0.45$, $p < 0.05$). However, the study demonstrated that at the end of the foreign body reaction the artificial tissue layer which covers the CVPS after implantation due to foreign body reaction shows only low reactivity towards infections.

Keywords: Encapsulation, infection, central venous access system, biomaterial

1. Introduction

Totally implantable long-term central venous port systems (CVPS) are widely used as a permanent means of accessing the vascular system for intravenous delivery of drugs [9, 11, 30], parenteral nutrition, blood transfusion, and blood sampling [4, 5, 7, 11]. These systems allow easy and repetitive puncture

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without causing much damage to the vessel walls. In the United States, approximately 5×10^5 of these devices are inserted every year [22]. All forms of implantation involve a certain degree of tissue injury, which induces a physiological healing response. This consists of two essential components: inflammation and repair processes that represent a spectrum of interdependent molecular and cellular responses. In the case of an implant, its foreign nature tends to induce an inflammatory response leading to the formation of a fibrous tissue capsule around the implant. Thickness and cellular morphology of the encapsulation tissue are functions of the implant shape [31], the surface texture of the implant [27], and the materials used for implant construction. If the implant is not biocompatible tissue response will consist of large numbers of cells surrounded by a looser matrix of collagen and fibroblasts [18, 26]. Tissue response is more pronounced in the course of a bacterial infection [14]. The rate of catheter related infections in CVPS ranges from 0.6 to 27% [15, 32], depending on catheter type and location and the patient's constitution. Immunosuppressed patients with port systems were found to have a median of 0.2 infections per 1000 port-days [6].

This study was designed to investigate the effect of bacterial infections on the tissue reaction induced by implanted venous access ports in adult patients.

2. Materials and methods

2.1. Patients and CVPS implantation

This study received research ethics committee approval from the relevant Research Ethics Committee of the Charité Clinic, Berlin. 25 patients (11 men, 9 women, average age: 58 yrs) were referred for enrolment in this study. All patients provided written informed consent after interview and eligibility assessment. Any patient requiring a CVPS, whatever the indication, was included in this trial. The samples were anonymised before testing.

Polyurethane CVPS (ChemoSite^{TM}, Covidien, Mansfield, USA) were implanted by direct puncture of the subclavian or jugular vein using combined ultrasound and fluoroscopy technique [10, 28]. Indications for port implantation included systemic chemotherapy, long-term antibiotic treatment, or bone marrow transplantation. Implantations were carried out under local anaesthesia and mild sedation, or general anaesthesia if the CVPS was implanted in the course of other surgery. The correct position of the tip of the catheter in the upper vena cava was verified by fluoroscopy. The reservoir was implanted on the right side in the prepectoral subcutaneous space. The system was then flushed and connected to a perfusion of a 0.5% solution of heparin (5000 IU/l – 42 ml/h) for 24 hours. Routine administration of preoperative antibiotics was not prescribed. Radiographs of the thorax were obtained after the operation for all patients. The CVPS was used for its designated purpose (e.g., chemotherapy, parenteral nutrition, and hydration) the day after intervention.

2.2. Histology

The samples were retrieved from patients which required port explantation due to port related infections (group A, 5 men, 1 women, average age: 68 yrs) or other reasons such as termination of treatment, thrombosis, CVPS dysfunction (group B, 6 men, 8 women, average age: 60 yrs) 299.9 ± 261.2 days after implantation. A sample of the encapsulating tissue covering the port body (see Fig. 1) together with surrounding tissue (at least 1×1 cm^2) was placed in a small container with fixing agent, a buffered neutral

4% formalin solution (pH 7). Histological sections of the samples were performed for light microscopic analysis after paraffin embedding. Sections were 3 μm thick and stained with haematoxylin and eosin, Weigert´s elastic stain, and Heidenhain's azan stain according to standard procedures [19].

2.3. Microscopy

Histological examination was performed using phase contrast mode, based on transmitted light microscopy (Oberver.D1, Zeiss), and AxioVision (Zeiss) imaging software. Cell density was determined as average number of cell nuclei in five different visual fields ($300 \times 300\,\mu m^2$, primary magnification 20-fold). Thickness of the fibrous capsule was measured as average of eight different measurement points which were distributed evenly over the tissue sample. The percentages of both the elastic and the collagenous connective tissue were quantified by the intensity of the particular stain. The sample that showed the most intensive stain of the particular tissue was defined to be the 100%-comparative sample.

2.4. Statistics

For all quantification analysis, results were expressed as means ± standard deviation of at least three independent experiments. Significance of differences was assessed using two-tailed Student´s *t*-test for unpaired samples. In case of multi-sample comparison, variance analysis was performed. Significance was assumed if p values were less than 0.05.

3. Results

In all patients of study group A and B a fibrous capsule covered the CVPS one year after its implantation, with the capsule tissue not adhering to the CVPS (see Fig. 1).

Histological analysis showed that the fibrous capsules of the patients with and without CVPS related infections did not differ in terms of the capsule thickness. Moreover, the elastin and collagen content of the fibrous capsules and the number of cells and capillaries of the fibrous capsule tissue were comparable (see Fig. 2).

However, a positive correlation between the cell density and the number of capillaries in the CVPS encapsulating tissue of all patients was observed (Fig. 3).

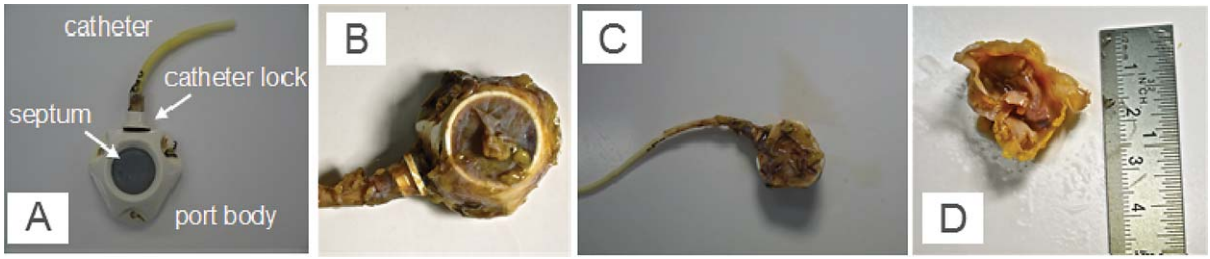

Fig. 1. Explanted CVPS; A: CVPS prior to implantation, B, C: CVPS with adhering surrounding tissue; D: CVPS encapsulating tissue after CVPS removal; samples fixed with 4% formalin for 12 hrs.

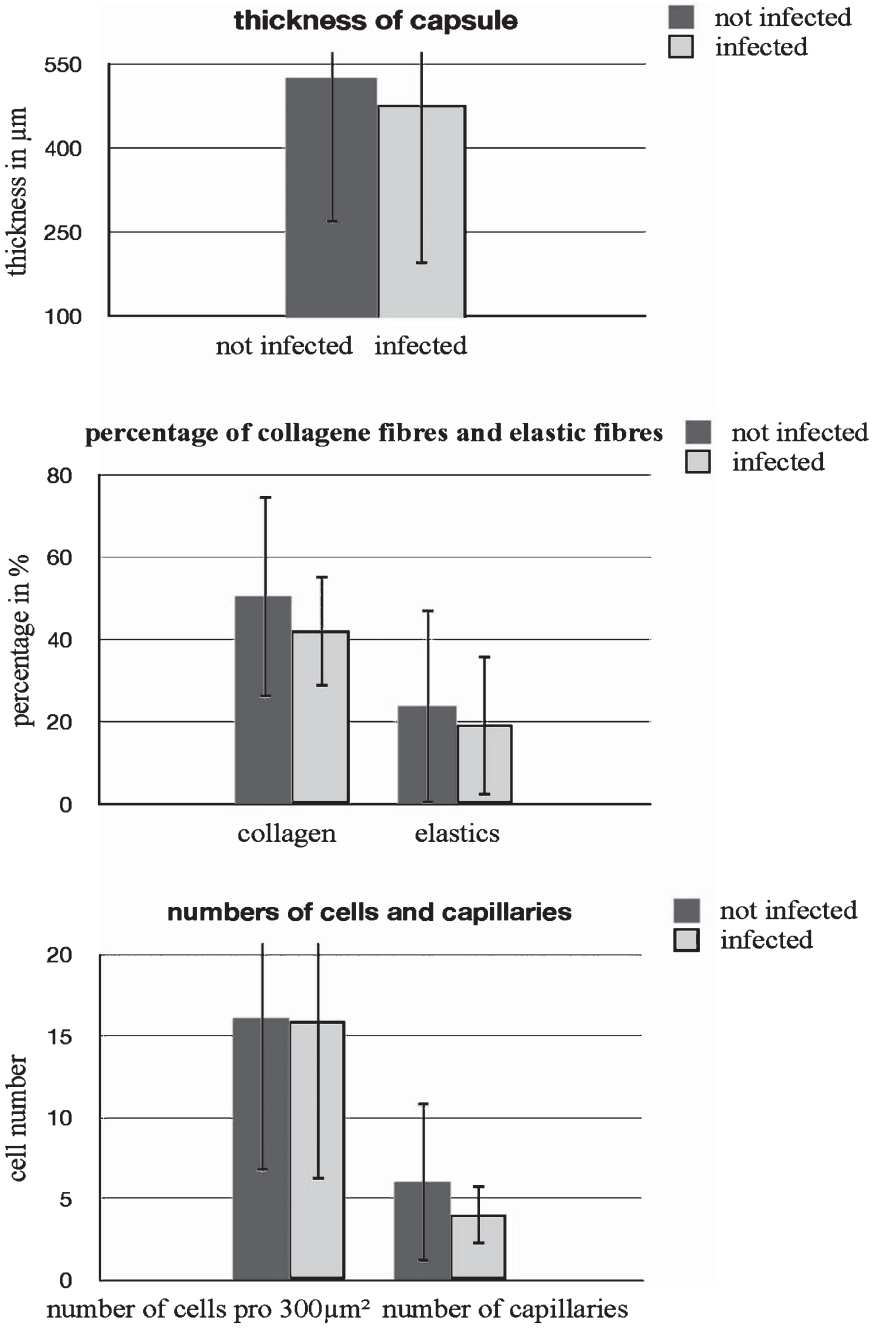

Fig. 2. CVPS encapsulating tissue with and without infection with regard to encapsulating tissue thickness, percentage of collagen or elastic fibers, and density of cells and capillaries.

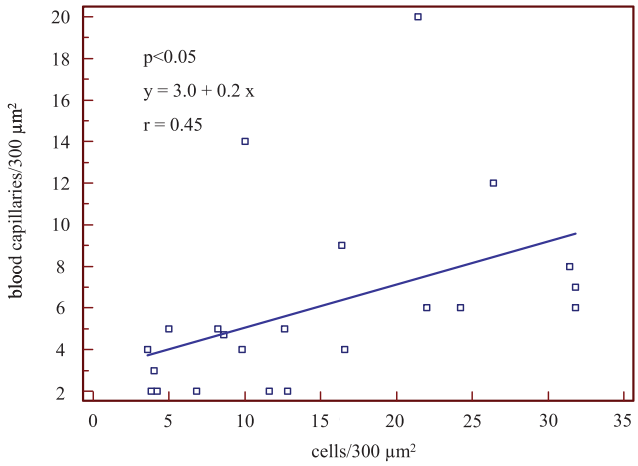

Fig. 3. Correlation between cell density (cells/300μm^2) and the number of capillaries in the CVPS encapsulating tissue.

4. Discussion

In a recent study, implantable venous access systems in 1500 patients with an average catheter life of 284 patient-days were examined, and port system-related complications were identified in 12.8% of the subjects [15]. The most common complication (4.8%) was found to be infection during postoperative use [15]. These data confirm findings from other studies with CVPS-associated infection rates ranging from 0.6–27% [1, 2, 13, 16, 24, 32]. It has been reported frequently that acute and subacute inflammation after CVPS implantation can be enhanced by bacterial infections at the implantation site [11, 14]. However, only few reports are available on the effect of bacterial infection of the implantation site and its ensuing scare tissue which is formed towards the end of the inflammation. The study presented here was designed to investigate the effect of bacterial infection on the artificial fibrous tissue layer which forms around the CVPS after implantation due to foreign body reaction involving inflammatory cells, giant cells, and fibroblasts with collagenous cicatrix formation.

Almost one year (299.9 ± 261.2 days) after CVPS implantation, the capsule which formed around the CVPS due to foreign body reaction was not affected by infection. There were no significant differences between patients with or without CVPS-related infections of the implantation site in terms of the capsule thickness, the content of the main extracellular matrix components elastin and collagen within the capsule tissue, or the cell density. Moreover, microvascularization and capillary density of the capsule tissue were not affected by infection of the CVPS implantation site either. Due to the wound healing reaction involving angiogenesis and fibroblast activation [11] there was a positive correlation between fibroblast density and number of capillaries in the capsule.

Since fibrous capsules covering implants can cause clinical complications and may affect implant functionality (e.g. by decreasing the diameter of the opening of the CVPS catheter tip), numerous efforts have been made to develop biomaterials that limit fibrous capsule formation [21]. Polymers, e.g. Shape memory polymers [17, 25], allow for tissue-adopted surface structure and surface charge composition, features which affect the degree and character of the induced fibrous capsule [8, 12]. However, very different implant materials induce surprisingly similar tissue reactions *in vivo* [3, 20, 23, 29] and further

studies have to be performed to get a more detailed knowledge about the impact of biomaterials on the formation of the fibrous capsule at the end of the foreign body reaction.

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