RIITTA RAUTIO

Endovascular Treatment of Peripheral Low-flow Vascular Malformations

Clinical, Radiological and Economic Results

ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty of Medicine of the University of Tampere,
for public discussion in the small auditorium of Building K,
Medical School of the University of Tampere,
Teiskontie 35, Tampere, on January 8th, 2005, at 12 o’clock.
ACADEMIC DISSERTATION
University of Tampere, Medical School
Tampere University Hospital, Department of Diagnostic Radiology
Finland

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Distribution
Bookshop TAJU
P.O. Box 617
33014 University of Tampere
Finland

Cover design by
Juha Siro

Printed dissertation
Acta Universitatis Tamperensis 1055
ISBN 951-44-6165-7
ISSN 1455-1616

Electronic dissertation
Acta Electronica Universitatis Tamperensis 404
ISBN 951-44-6166-5
ISSN 1456-954X
http://acta.uta.fi

Tampereen Yliopistopaino Oy – Juvenes Print
Tampere 2004
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<td>ABC</td>
<td>activity based cost analysis</td>
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<tr>
<td>AV</td>
<td>arteriovenous</td>
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<td>AVM</td>
<td>arteriovenous malformation</td>
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<td>CIVIQ</td>
<td>the chronic venous insufficiency questionnaire</td>
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<td>CT</td>
<td>computed tomography</td>
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<td>DSA</td>
<td>digital subtraction angiography</td>
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<td>GDC</td>
<td>Guglielmi detachable coil</td>
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<td>ISSVA</td>
<td>International Society for the Study of Vascular Anomalies</td>
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<tr>
<td>MR</td>
<td>magnetic resonance</td>
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<td>MRA</td>
<td>magnetic resonance angiography</td>
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<td>MRI</td>
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<td>MRPA</td>
<td>magnetic resonance projection angiography</td>
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<td>NBCA</td>
<td>N-butyl cyano-acrylate</td>
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<td>PTA</td>
<td>percutaneous transluminal angioplasty</td>
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<td>PVA</td>
<td>polyvinyl alcohol</td>
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<td>RAND-36</td>
<td>Rand 36-item health survey</td>
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<td>SF-36 Mos</td>
<td>36-item short form health survey</td>
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<tr>
<td>SIP</td>
<td>Sickness Impact Profile</td>
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<td>T1</td>
<td>longitudinal relaxation</td>
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<td>T2</td>
<td>transverse relaxation</td>
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<td>US</td>
<td>ultrasound, ultrasonography</td>
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ABSTRACT

The purpose of this study was to evaluate the results of endovascular sclerotherapy for low-flow vascular malformations and to report the long-term results as well as the quality of life of these patients after treatment. The evaluation of the costs of endovascular therapy from the viewpoint of the interventional unit was also performed by using Activity Based Cost Analysis.

Fifty-eight patients with peripheral venous or lymphatic (low-flow) malformations treated by endovascular therapy compose the present study population. The study population includes 44 patients with peripheral venous malformations treated mainly with ethanol sclerotherapy and 14 patients with lymphatic malformations, all of whom were treated by OK-432 sclerotherapy. The patients were asked to attend a clinical follow-up visit. To evaluate the quality of life after treatment, all patients with venous malformations were asked to complete a questionnaire which included 20 multiple-choice questions exploring four dimensions: psychological, physical and social functioning and pain. The patients with venous malformations in the face and neck were examined with MR imaging at the same visit. All the pre-treatment and post-treatment images were reviewed.

Endovascular therapy for low-flow vascular malformations was found to be well tolerated, with minimal complications. MRI was found to be appropriate pre-treatment imaging method, in order to characterize the lesion, evaluate its extent and reveal possible high-flow components. Several factors were discovered in the study, which may have an impact in the future when planning the endovascular therapy of venous malformations and may help in predicting the treatment results. The questionnaire on quality of life was found to evaluate patients’ state of health after treatment more objectively than purely subjective opinion. Those patients younger than 16 years at the beginning of treatment had better quality of life, likewise those who were clinically followed up by physicians specialized in vascular malformations. Clinical control performed by physicians specialized in vascular malformations was found to be the most appropriate method of follow-up. In certain cases imaging control is needed; especially when clinical examination may be more complicated regarding possible small residual lesions, especially in anatomically difficult locations such as face and neck. In these circumstances MR imaging is the preferrable imaging.

The cost analysis revealed that in general endovascular treatment is an expensive method of treatment due to the high cost of materials. However, endovascular treatment of low-flow malformations is different, being distinctly the cheapest method of endovascular treatment when the costs are analyzed from the viewpoint of the interventional unit. In cases where microcatheter embolization is needed due to high-flow components in the malformation, the costs are added up.
1. INTRODUCTION

Congenital vascular malformations do not regress spontaneously and they grow simultaneously with the child. On the basis of their pathological structures they are subcategorised as arterial, capillary, venous and lymphatic malformations (Mulliken and Glowacki 1982). Various combinations of malformations are quite common. In clinical practice vascular malformations are classified as either low-flow or high-flow lesions. Malformations with arterial components are considered to be high-flow lesions (Rak et al. 1992, Fishman and Mulliken 1998, Donnelly et al. 2000).

Treatment is indicated when venous malformations cause severe cosmetic distress, pain or functional problems (Dubois and Garel 1999, Dubois and Garel 2002). For lymphangiomas treatment is indicated due to the extremely serious complications that may appear if they are left untreated; bleeding and infection can rapidly increase the size and threaten vital functions (Filston 1994, Luzzatto et al. 2000, Orvidas and Kasperbauer 2000).

Treatment options include elastic compression garments, surgery and embolotherapy with a fibrosing material (Jackson et al. 1992). Nonsurgical treatment with diathermy and radiation therapy has been attempted for the treatment of lymphangiomas (Greinwald et al. 1999). Complete surgical excision is seldom achieved, because vascular malformations grow among soft tissues such as muscles, nerves and blood vessels and are difficult to delineate during surgery. In many cases, they are anatomically difficult to reach surgically or are in inaccessible areas. Cosmetic deformity may also result from the excision (Werner et al. 2001). Therefore other treatment options, especially endovascular treatment, have aroused interest. The results of sclerotherapy of venous malformations with various sclerosing agents have been reported, but only few long-term follow-ups.

Recently there have been promising results from treating lymphangiomas of the head and neck region with a new sclerosant, OK-432. OK-432 is a lyophilized biological preparation containing the cells of Streptococcus pyogenes Su-strain treated with benzylpenicillin. The first results of intralesional injection of OK-432 as treatment for lymphangiomas were reported in 1987 (Ogita et al. 1987). Tampere University Hospital was the first Finnish hospital to use this sclerosant for endovascular treatment of lymphangiomas.

Interventional radiology has greatly increased in the course of the last 20 years. Various new endovascular techniques have appeared, like vascular embolizations with microcatheter technique and sclerotherapies. These new tools have brought new treatment options for diseases. On the other hand this has added to the burden and expenses of the radiological units. The health care organizations and policy makers are increasingly concerned about the costs of health care. However, analyses dealing with interventional radiology have rarely been published, though radiological interventions have increased
in number and techniques. Activity-based cost analysis (ABC) has been used in many service organizations and achieved great benefits when planning activity and budget, because the costs can then be more precisely allocated to their resources and also the cost factors of the activities that form the product can be evaluated (Kaplan and Cooper 1998).
2. REVIEW OF THE LITERATURE

2.1. Classification of vascular anomalies

The lack of appropriate classification for vascular anomalies has long been a source of confusion, including various descriptive and histological terminology. The classification accepted by ISSVA (International Society for the Study of Vascular Anomalies) was described by Mulliken and Glowacki in 1982. This system separates vascular anomalies clearly into two, namely hemangiomas and vascular malformations, on the basis of their clinical behavior, physical findings, histological findings and cellular kinetics. This rational classification helps to understand the nature of the lesions and so provides the prediction of natural evolution, the choice of treatment and response to treatment. A proper identification also helps to alleviate patients’ and parents’ anxiety and to make a prognosis.

2.1.1. Hemangiomas

Hemangiomas are benign tumours, characterized by increased endothelial proliferation. Although no clear evidence exists regarding the causes of the appearance of hemangiomas, some recent studies have suggested chromosomal abnormalities (Brouillard and Vikkula 2003). It is known that hemangioma endothelial cells express placenta-associated markers such as glucose 1 transporter (glut-1), that may be helpful in differential diagnosis for other vascular tumours (Enjolras 2003).

Hemangiomas are the most common soft tissue tumours in infancy. They are found with greater frequency in girls, caucasians, premature infants and twins (Mulliken and Glowacki 1982, Enjolras et al. 1990, Fishman and Mulliken 1993, Gorlin et al. 1994, Achauer et al. 1997, Burrows et al. 1998). The majority appear during the first weeks of life and grow rapidly during the first year. At least 60% of hemangiomas are located in the face and neck region, 25% in the trunk and 15% in the extremities. Most hemangiomas subside spontaneously by the age of five to seven years (Fishman and Mulliken 1998, Dubois and Garel 1999, Donnelly et al. 2000, Dinehart et al. 2001).

2.1.2. Vascular malformations

Vascular malformations are congenital collections of abnormal vascular structures with normal endothelium. They are congenital lesions but are not always evident at birth. Most appear to be sporadic, but they may also be inherited, in which case multiple lesions are frequent (Boon et al. 1994, Gallione et al. 1995, Brouillard and Vikkula 2003). Several causative factors have been identified for molecular causes of vascular malformations (Brouillard and Vikkula 2003). They grow commensurately with the child and do not regress spontaneously. On the basis of their pathological structures vascular malformations are subcategorised as: arterial, capillary, venous, and lymphatic malformations. Various mixed, combined malformations also exist (Burrows et al. 1998, Fishman and Mulliken 1998).
Venous malformations are the most common of all vascular anomalies (Fishman and Mulliken 1998). The main locations for venous malformations are the head and neck (40%), the extremities (40%) and the trunk (20%) (Dubois and Garel 1999).

No evidence for inheritance of lymphatic malformations exists, indicating that if genetic alterations play a role in their pathogenesis, germline mutations are lethal and sporadic lesions may occur as a result of “localized” somatic mutations (Brouillard and Vikkula 2003). Half of lymphangiomas are diagnosed at birth and 90% in children before the age of 2 years (Zadvinskis et al. 1992, Borecky et al. 1995, Vazquez et al. 1995). Approximately 75% of lymphangiomas are located in the neck region, some of them growing into the mediastinum (Meza et al. 1993). Cystic lymphatic malformations may be subdivided into macrocystic, microcystic and mixed forms.

In clinical practice the most important characterizing feature is whether the lesion is either a low-flow or a high-flow vascular malformation. Lesions with arterial components are considered to be high-flow malformations. Capillary, venous, lymphatic malformations and their combinations are considered to be low-flow lesions (Rak et al. 1992, Fishman and Mulliken 1998, Donnelly et al. 2000).

2.1.3. Various syndromes

In a review of the genetic literature, Burns et al. (1991) pointed out that dysmorphic syndromes are commonly (incorrectly) reported to be associated with hemangiomas, when in fact they are vascular malformations.

It is also of paramount importance to eliminate the possibility of rare malignant vascular tumours (kaposiform hemangioendothelioma, tufted angioma, Kaposi's sarcoma and angiosarcoma) when examining a patient with a vascular lesion (Blei 1999).
2.2. Clinical manifestations of vascular anomalies

The clinical manifestations of vascular anomalies may vary greatly. Hemangiomas most often appear as subcutaneous bluish-red masses reminiscent of the surface of a strawberry. The clinical appearance varies with the degree of dermal involvement and the depth of the lesion (Waner et al. 1992, Fishman and Mulliken 1993, Dubois and Garel 1999, Rodesch 2000).

2.2.1. Low-flow malformations
The majority of venous malformations are asymptomatic. When symptomatic, they may be cosmetically deforming, cause pain, induce neuropathy, ulcerate, induce changes of abnormal bone growth, cause pathologic fractures, bleed or compress or invade adjacent structures. Symptoms usually appear in childhood and become more severe as the child grows. They may show enlargement with the Valsalva maneuver, when in dependent position or when the child cries or strains. When visible, they are generally soft with a bluish discoloration. Symptoms are related to size and location. In the extremities the venous malformations are typically cosmetically disfiguring and cause pain and swelling. This is aggravated by strain or when the lesion is in a dependent position. Cervicofacial venous malformations may cause facial asymmetry and progressive anatomical distortions, and also impede speech and swallowing and obstruct the upper airway. Exacerbation may follow after trauma, during sepsis or at the time of hormonal changes, e.g. on puberty or at pregnancy (Lasjaunias and Berenstein 1987, Jackson et al. 1993, Yakes 1994, Fishman and Mulliken 1998, Dubois and Garel 1999, Donnelly et al. 2000, Dubois et al. 2001, Johnson et al. 2002).

Lymphangiomas are usually asymptomatic and non-tender tumours that grow slowly. As their size increases they may cause cosmetic impairment or interfere with breathing and swallowing (Orvidas and Kasperbauer 2000). Bleeding and infection may rapidly increase the size and threaten vital functions (Filston 1994).

2.2.2. High-flow malformations
High-flow malformations are rare and the majority of them are dormant during infancy and childhood. In clinical examination the lesion may appear blue and one may feel a pulsatile mass. These lesions grow with the child and can enlarge rapidly due to thrombosis, infection and hormonal stimulation. Possible symptoms and signs include congestive heart failure, embolism, pain, bleeding and ulceration (Burrows et al. 1998, Fishman and Mulliken 1998, Kohout et al. 1998).

2.2.3. Various syndromes
All dysmorphic syndromes share a propensity for soft tissue and skeletal overgrowth. Clinicians should be aware of at least three of these rarities: Klippel-Trenaauay syndrome signifies a combined low-flow capillary lymphaticovenous malformation associated with
hypertrophy of a limb or trunk. Hypertrophy of a limb may be minor to grotesque. Proteus syndrome is a vascular, skeletal and soft tissue disorder that has its defining characteristic asymmetric overgrowth and gigantism. Parkers Weber syndrome patients have the lower limb more often than the upper extremity involved. Brightly stained skin, warmth, bruit and thrill are pathognomonic. Shunting may be so extreme that infants are born with congestive heart failure (Fishman and Mulliken 1998).

Kasabach-Merritt syndrome is the association of a severe consumptive coagulopathy with a soft tissue vascular tumour. Kasabach-Merritt syndrome is a medical emergency which requires aggressive treatment (Abernethy 2002).

2.3. Diagnosis of vascular anomalies

2.3.1. Clinical
In most instances the diagnosis can be established on clinical examination and accurate patient history. In spite of that, too many patients with vascular malformations have been misinformed that their lesions are hemangiomas and will probably resolve with time. This may create gratuitious emotional problems and confusion as well as inappropriate treatment in some cases.

2.3.2. Radiological
The need for diagnostic imaging appears when a lesion is atypical in appearance or presentation or when it is located so deep that it is difficult to assess by means of physical examination (Paltiel et al. 2000). Radiological evaluation is required to accurately evaluate the extent and nature of the lesion and to plan appropriate treatment. The most important feature is whether the malformation is a low-flow or high-flow lesion (Donnelly et al. 2000).

Modern imaging techniques have made a great contribution to the accurate diagnosis of vascular anomalies; MRI and color doppler ultrasound are non-invasive imaging techniques, and have mainly displaced conventional angiography for diagnostic purposes.

Conventional radiography plays a minor role in the diagnosis and classification of vascular malformations. It is needed if bone or joint involvement is suspected. Large hemangiomas or vascular malformations may cause growth disturbance in adjacent long bones (Abernethy 2003).

2.3.2.1. Ultrasound
Ultrasound is ideal when examining children with suspected vascular lesions, because it is painless and non-invasive. It is most appropriate when examining superficial lesions. Its value, however is limited to certain anatomical locations, like the thorax or in the vicinity of the airway or gastro-intestinal tract, because ultrasound cannot penetrate bone
Hemangiomas typically show an appearance of a well-defined, solid, echogenic mass, which is intensely hypervascular (Dubois and Garel 1999, Abernethy 2003). In contrast to hemangiomas, grey-scale ultrasound reveals hypoechoic structures of the vascular spaces in cases of venous malformations (Dubois et al. 1998, Dubois and Garel 1999, Trop et al. 1999, Paltiel et al. 2000). Color flow imaging shows slow, turbulent flow within dilated compressible vascular spaces in most venous malformations (Abernethy 2003).

Gray-scale US may help in the differential diagnosis of venous malformations and lymphangiomas. The detection of phleboliths will provide a diagnosis of venous malformations. However, few venous malformations display intrallesional calcifications, which diminishes the usefulness of this criterion (Trop et al. 1999). Macrocystic lymphangiomas appear as large, anechoic cavities separated by septa in grey-scale ultrasound. Microcystic lymphangiomas are hyperechoic, without visible channels in grey-scale ultrasound.

Doppler ultrasound has been proved by various authors to nicely differentiate low-flow lesions from high-flow lesions (Dubois et al. 1998, Dubois and Garel 1999, Trop et al. 1999, Donnelly et al. 2000, Dubois et al. 2001, Abernethy 2003). Paltiel et al. (2000) reported the accuracy of ultrasound to distinguish hemangiomas from vascular malformations. However, they made no attempt to assess the distinction from vascular anomalies to other soft-tissue masses. Dubois et al. (2002) reported on 16 infants with vascular tumors where they were able to differentiate vascular tumors from hemangiomas with doppler sonography in all cases except one. Hemangiomas appeared with high vessel density and high peak arterial Doppler shift. The drawbacks of US are limited ability to visualize the whole extent of a large lesion and operator dependence (Fordham et al. 2000).

2.3.2.2. Magnetic resonance imaging and computed tomography
MRI displays the extent of the lesion and its relationship to adjacent structures like muscles, tendons and nerves. The capacity of multiplanar imaging and great sensitivity to high-velocity blood flow have shown MRI to be extremely valuable for imaging vascular anomalies (Meyer et al. 1991, Rak et al. 1992, Kim et al. 1999, Abernethy 2003). All these studies were based on the findings that presence or absence of flow voids characterize vascular malformations.

The most valuable information from a MRI study when examining a suspected vascular anomaly is gained from a combination of T1-weighted, fat-saturated T2-weighted and gradient-echo (flow-weighted) MR images. The axial plane is the most useful in depicting the anatomical structures and tissue planes, with additional help from coronal or sagittal images (Donnelly et al. 2000).
MR imaging of proliferating hemangiomas often show relatively well-defined, lobulated solid mass with high signal intensity in T2-weighted and intermediate signal intensity on T1-weighted images. There is usually intense and uniform enhancement following intravenous gadolinium (Meyer et al. 1991, Kern 2000, Abernethy 2003).

Venous portions of a malformation will appear as a collection of serpentine structures separated by septations. Venous malformation may present variable signal intensity on T1-and T-2 weighted sequences because of hemorrhage and thrombosis. Most often, however, they present intermediate signal intensity on T1 and high signal on T2 (Gelbert et al. 1991, Hovius et al. 1996, Dubois et al. 2001). Small punctuate areas of high signal intensity may be present and these are caused by hemorrhage and thrombosis (Cohen et al. 1986, Abernethy 2003). Gadolinium-enhanced T1-weighted images may show enhancement of the slow-flowing venous channels (Meyer et al. 1991).

Rak et al. (1992) performed a retrospective study of symptomatic peripheral vascular malformations to further determine the distinction between slow-flow venous malformations and high-flow malformations. They found that venous malformations had a propensity for multifocal involvement, orientation along the long axis of the extremities or affected muscles and adherence to neurovascular distributions. High-flow malformations showed muscle atrophy and subcutaneous fatty prominence.

Most patients with lymphatic malformations do not have diagnostic problems, because these malformations present early in childhood and are typically located in the neck and axilla (Meza et al. 1993). Venous malformations, however, may be difficult to differentiate from lymphatic malformations in MRI, but contrast-enhanced images improve the accuracy of the diagnosis, because venous components enhance slowly but lymphatic cysts do not enhance if contrast is administered (Meyer et al. 1991, Kern et al. 2000). Internal septations and walls of lymphangiomas may enhance if contrast is administered and this is characteristic for lymphangiomas (Meza et al. 1993, Borecky et al. 1995, Konez et al. 2002).

2.3.2.3. Imaging of the flow
The value of MR imaging with contrast medium has been further evaluated in several recent studies. Ziyeh et al. (2003) examined eight patients with vascular anomalies using time-resolved magnetic resonance projection angiography (MRPA). They found that high-flow arteriovenous malformations showed early, intense enhancement and venous malformations were either not visible on MRPA or showed late enhancement of veins.

Van Rijswijk et al. (2002) reported that by combining dynamic contrast-enhanced MR characteristics with morphological findings, it is possible to further differentiate the various peripheral vascular malformations. Late enhancement (>6s after arterial enhancement), absence of flow voids and the presence of dilated venous spaces were indicative of the
presence of pure venous malformations. Arterial or arteriovenous malformations showed early contrast enhancement (<6 s after arterial enhancement), and the presence of flow voids. Early enhancement, absence of flow voids and the presence of dilated venous spaces were indicative of capillary-venous malformations.

Though MRI and MR angiography differentiate high-flow components from low-flow components, it is inferior to conventional angiography for revealing vascular detail and for planning intervention, as Herborn et al. (2003) showed in their article.

CT does demonstrate the extent of the vascular malformation, but MR imaging is more accurate owing to its superior contrast resolution and so is more useful in determining tissue and blood flow characteristics. CT has some advantages as regards the visualization of calcification and skeletal or visceral involvement (Dubois et al. 2001, Abernethy 2003). CT also involves significant exposure to ionising radiation. CT is only indicated for some reasons when MRI cannot be used.

Digital subtraction arteriography is still the reference test for accurate separation of high-flow and low-flow lesions (Burrows et al. 1983), but less invasive diagnostic methods are desirable. DSA is particularly important in pre-operative assessment and before interventional procedures for high-flow lesions, because it allows optimal visualisation of arterial anatomy (Abernethy 2003). High-flow lesions show dilatation and lengthening of afferent arteries with early opacification of enlarged draining veins. Venous malformations may show a completely normal angiography, or only evidence of venous stasis is displayed (Burrows et al. 1983).

Direct puncture venography is necessary only when therapy is indicated. It is the best way to demonstrate the extent of the abnormal postcapillary vascular spaces and the draining veins of a venous malformation (Yakes 1994, Dubois and Garel 1999).

2.4. Treatment indications of vascular anomalies

Most hemangiomas subside spontaneously, so they require no treatment. A small percentage of them develop life-threatening complications, however. Active treatment is indicated if the lesion causes high-output congestive cardiac failure. Treatment is also essential if the lesion is in a special location causing severe problems in visual, nasal, laryngeal or acoustic functions (Jackson et al. 1993, Rodesch 2000).

Vascular malformations are congenital disorders that enlarge in proportion to the growth of the child, resulting in increasing symptoms and need for treatment (Mulliken and Glowacki 1982). Indications for treatment are pain, nerve damage, ulcerations, disfigurement, function disturbances, bleeding and heart failure (Dubois and Garel 1999, Dubois and Garel 2002).
Treatment is indicated for lymphangiomas, due to the extremely serious complications that may appear if left untreated. Spontaneous shrinkage may seldom occur. As their size increases they may cause cosmetic impairment or interfere with breathing and swallowing (Luzzatto et al. 2000, Orvidas and Kasperbauer 2000). Bleeding and infection can rapidly increase the size and threaten vital functions (Filston 1994).

Conservative treatment is the first choice for children with complex combined vascular malformations, including various devices such as shoe-lifts and elastic compressive stockings. Compression therapy may be helpful for protecting the involved limb, even from minimal trauma that can cause bleeding from the large superficial malformations. In general, surgery should not be undertaken to improve cosmetic disparity at the expense of function. Epiphysiodesis is performed, if necessary, as well as staged surgical contour resection or selective amputation in cases of major hypertrophy (Fishman and Mulliken 1998, Jacob et al. 1998). Active treatment is indicated if the lesion causes consumptive coagulopathy (Kasabach-Merritt syndrome) (Abernethy 2003).

2.5. Treatment options for vascular anomalies

2.5.1. Hemangiomas
Various therapies have been used in an attempt to treat hemangiomas when complications develop. The current first line treatment is systemic administration of corticosteroids (Enjolras et al. 1990, Dubois and Garel 1999, Berenstein 2003). Direct steroid injections are used for rapid control of orbital lesions (Abernethy 2003). If corticosteroid therapy fails, alpha-interferon can be used. This has, however, been associated with a rare irreversible neurologic spastic diplegia, and is now not very commonly used (Barlow et al. 1998). Laser therapy has proved valuable for superficial cutaneous and mucous as well as airway lesions (Blei 2002). Surgery and embolization may be used in refractory cases (Donnelly et al. 2000, Werner et al. 2001, Berenstein 2003).

2.5.2. Low-flow vascular malformations
The improved understanding of the flow characteristics of vascular malformations has led to more accurate treatment. The most important treatment options for low-flow malformations are surgery and endovascular therapy with a fibrosing material (Jackson et al. 1992).

For venous malformations elastic compression garments can also be used, but this is more symptomatic than therapeutic treatment. Nonsurgical treatment with diathermy and radiation therapy has been attempted for the treatment of lymphangiomas (Greinwald et al. 1999).
Complete surgical excision is seldom achieved, because vascular malformations grow among soft tissues such as muscles, nerves and blood vessels and are difficult to delineate during surgery. In many cases, they are in anatomically difficult or inaccessible areas for surgery. Hemostasis may be difficult to control during operation. Recurrence and cosmetic deformity are therefore common after excision (Werner et al. 2001). For these reasons other treatment options have aroused interest.

2.5.2.1. Sclerotherapy
For venous malformations sclerotherapy is the primary treatment, with or without surgical excision (Yakes et al. 1990, Jackson et al. 1992, Yakes 1994, Puig et al. 2003). Direct puncture allows direct access into the abnormal vascular compartment and the inflow arterial system and capillary bed are spared and tissue loss should be minimized (Yakes 1994). Superficial or easily palpable lesions may be punctured without imaging guidance, but fluoroscopy is always needed to verify the diagnosis and the needle placement in the lesion and to determine the volume of the venous malformation. The traditional method for procedural guidance has been contrast material injection with fluoroscopy after a blind needle stick (Svendsen et al. 1994, Shireman et al. 1997, Gelbert et al. 2000, Lee et al. 2001). It is likely that multiple blind needle sticks and poorly positioned needles increase the amount of perforations and extravasation of the sclerosant, so some new sophisticated ways to guide the needle to the optimal position have been developed.

Donnelly et al. (1999) reported recently a series of 24 percutaneous sclerosis procedures where they used real-time ultrasound guidance to directly visualize the needle placement and to facilitate direct cannulation of the vascular channels. They found it helpful to minimize the number of needle passes and thus the risk of extraluminal extravasation and the resultant rate of complications was reduced. They also found that visualization of the presence or absence of vascular channels on ultrasound helped them to predict the potential success of sclerosis procedures. Other authors have reported similar experiences for the advantage of ultrasound guidance (Yamaki et al. 2000, Jain et al. 2002, Cabrera et al. 2003), especially when the malformation is located deep in the soft tissues (Dubois et al. 2001).

Lewin et al. (1999) reported their preliminary experience with 14 procedures in MR guided sclerotherapy. The mean procedural time was 29 minutes. They injected a mixture of sclerosing agent (ethanolamine olate or sodium tetradecyl sulphate) and contrast material (gadopentate dimeglumine) with a concentration of 0.1 ml: 2 ml. The injection was monitored by means of continous gradient-echo MR imaging. The authors found that tracking the injected agent during treatment reduces the risk of subcutaneous or submucosal injection that can lead to tissue necrosis. MR guidance was also used with good treatment results in a recent report by Boll et al. (2004).
Another way to monitor the possible extravasation of sclerosant is to render the solution radiopaque by mixing the sclerosant with contrast, and injecting the sclerosant solution using fluoroscopic evaluation. Donnelly et al. (1999) and Goyal et al. (2002) used ethanol as sclerosant and Siniluoto et al. (1997) used sodium tetradsyl sulphate (Sotradecol®).

2.5.2.2. Sclerosing agents

There is a variety of different sclerosing agents, like absolute ethanol, sodium tetradsyl sulphate (Sotradecol®), alcohol solution of zein (Ethibloc®), polidocanol (Aetoxysclerol®) and ethanolamine olete, that have been used for the treatment of venous malformations. Ethibloc® is a fibrosing agent containing alcoholic solution and sodium diatrizoate that makes it opaque to X-rays without any need for additional contrast. The results of sclerotherapy of venous malformations during the past 10 years with different sclerosants are summarized in Table 1. Articles based on experience of less than five patients are not included. The most common self-limiting minor complications reported by most authors included skin necrosis, skin blistering, transient pain and transient swelling occasionally inducing transient nerve compression. Ethanol is the most commonly used sclerosing agent (Dubois et al. 1991) and has been reported to be the most reliable sclerosant (Shireman et al. 1997, Siniluoto et al. 1997).

In the past lymphangiomas were always surgically treated, and even today, with the many treatment options available, surgery is often the first choice. Surgery still carries a complication rate of 12-33 % and a recurrence rate of 15-53 %, so other methods of treatment are desirable (Chait 1974, Nihn and Nihn 1974, Kennedy 1989, Hancock et al. 1992). The idea of treating lymphangiomas with sclerosing agents is old. At the beginning of the century it was noticed that after spontaneous infection, lymphangiomas might shrink or even completely regress (Luzatto et al. 2000).

Intralesional injection of various sclerosing agents such as alcohol, alcohol solution of zein (Dubois et al. 1997), boiling water, hypotonic saline (Nihn and Nihn 1974) bleomycin (Orford et al. 1995), 50 % dextrose (Hancock et al. 1992), and triamcinolone (Farmand and Kuttenberger 1995) have been used to replicate what may occur spontaneously, but none has acted as expected. These sclerosants may spread outside the thin-walled lesions and cause damage to the surrounding structures making subsequent surgery even more complicated because of extensive scarring. Due to their limitations the use of sclerosing agents has met with only limited success.

Recently there have been promising results from treating lymphangiomas of the head and neck region with a new sclerosant, OK-432 (Picibanil®) (Ishida and Hoshino 1985). OK-432 is a lyophilised biological preparation containing the cells of Streptococcus pyogenes Su-strain treated with benzylpenicillin. It has been used extensively as immunotherapy for malignant tumours in Japan. The first results of intralesional injection of OK-432 as treatment for lymphangiomas were reported by Ogita et al. (1987). When injected into
the cystic spaces it produces sclerosis that does not spread outside the lesion. No necrosis is seen histologically although the OK-432 induces inflammations and activation of necrotizing cytokines (Ogita et al. 1996). Adverse effects of treatment are limited to mild post injection pyrexia (Ogita et al. 1994). The reports of OK-432 therapy for lymphangiomas are summarized in Table 2. Articles reporting on five or a smaller number of patients are not included.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Nr of patients</th>
<th>Treatment</th>
<th>Results</th>
<th>Major complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Svendsen et al. 1994</td>
<td>44</td>
<td>ethanol and surgery</td>
<td>excellent or good</td>
<td>tissue necrosis requiring surgery: 2</td>
</tr>
<tr>
<td>Yakes 1994</td>
<td>36</td>
<td>ethanol</td>
<td>improved</td>
<td>muscle contractures, nerve injury, deep vein thrombosis, pulmonary embolism, cardiopulmonary collapse</td>
</tr>
<tr>
<td>DeLormier 1995</td>
<td>34</td>
<td>sodium mornhaute, sodium tetradecyl sulphate, ethanolamine, ethanol</td>
<td>satisfied</td>
<td>anaphylaxis</td>
</tr>
<tr>
<td>Shireman et al. 1997</td>
<td>12</td>
<td>ethanol</td>
<td>resolved or regressed</td>
<td>no major</td>
</tr>
<tr>
<td>Siniluoto et al. 1997</td>
<td>38</td>
<td>sodium tetradecyl sulphate and surgery</td>
<td>excellent or good</td>
<td>unilateral blindness: 1</td>
</tr>
<tr>
<td>Pappas et al. 1998</td>
<td>57</td>
<td>ethanol and surgery</td>
<td>reduction</td>
<td>acute visual impairment requiring canthotomy: 1</td>
</tr>
<tr>
<td>Berenguer et al. 1999</td>
<td>40</td>
<td>ethanol, sodium tetradecyl sulphate and surgery</td>
<td>cured or marked</td>
<td>permanent unilateral vocal cord paralysis: 1</td>
</tr>
<tr>
<td>Gelbert et al. 2000</td>
<td>23</td>
<td>alcoholic solution of zein, polidocanol and surgery</td>
<td>improved</td>
<td>inflammatory reaction requiring surgery: 3</td>
</tr>
<tr>
<td>Yamaki et al. 2000</td>
<td>28</td>
<td>polidocanol and surgery</td>
<td>disappeared or decreased</td>
<td>no major</td>
</tr>
<tr>
<td>Choi et al. 2002</td>
<td>29</td>
<td>ethanolamine olate, coil embolization and surgery</td>
<td>effective or beneficial</td>
<td>no major</td>
</tr>
<tr>
<td>Goyal et al. 2002</td>
<td>59</td>
<td>ethanol</td>
<td>excellent or good</td>
<td>tissue injury requiring surgery: 6, deep vein thrombosis: 5, acute pulmonary embolism: 1, permanent nerve damage: 2, muscle contraction requiring surgery: 1</td>
</tr>
<tr>
<td>Johnson et al. 2002</td>
<td>7</td>
<td>ethanol and surgery</td>
<td>improved</td>
<td>swelling requiring intubation: 1, swelling requiring a nasogastric tube: 1</td>
</tr>
<tr>
<td>Cabrera et al. 2003</td>
<td>50</td>
<td>polidocanol</td>
<td>beneficial</td>
<td>no major</td>
</tr>
<tr>
<td>Lee et al. 2003</td>
<td>87</td>
<td>ethanol</td>
<td>improved</td>
<td>no major</td>
</tr>
</tbody>
</table>

Table 1. Sclerotherapy of venous malformations.

<table>
<thead>
<tr>
<th>Author</th>
<th>Nr of patients</th>
<th>Prior treatment</th>
<th>Results</th>
<th>Major complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ogita et al. 1987</td>
<td>9</td>
<td>surgery:</td>
<td>2 cured or improved:</td>
<td>9 no</td>
</tr>
<tr>
<td>Ogita et al. 1994</td>
<td>64</td>
<td>surgery:</td>
<td>14 cured or marked shrinkage:</td>
<td>38 no</td>
</tr>
<tr>
<td>Schmidt et al. 1996</td>
<td>11</td>
<td>surgery:</td>
<td>4 cured or improved:</td>
<td>9 no</td>
</tr>
<tr>
<td>Smith et al. 1996</td>
<td>6</td>
<td>surgery:</td>
<td>7 cured:</td>
<td>2 no</td>
</tr>
<tr>
<td>Brewis et al. 1999</td>
<td>11</td>
<td>surgery:</td>
<td>6 cured or marked:</td>
<td>4 one abscess</td>
</tr>
<tr>
<td>Greinwald et al. 1999</td>
<td>13</td>
<td>surgery:</td>
<td>5 cured or improved:</td>
<td>5 no</td>
</tr>
<tr>
<td>Luzzatto et al. 2000</td>
<td>15</td>
<td>surgery:</td>
<td>5 cured or marked:</td>
<td>10 no</td>
</tr>
<tr>
<td>Sung et al. 2001</td>
<td>21</td>
<td>surgery:</td>
<td>5 cured or marked:</td>
<td>15 no</td>
</tr>
<tr>
<td>Claesson and Kuylenstierna 2002</td>
<td>32</td>
<td>surgery:</td>
<td>1 excellent:</td>
<td>26 no</td>
</tr>
</tbody>
</table>

Table 2. Sclerotherapy results of OK-432 treatment for lymphangiomas.

2.5.3 High-flow vascular malformations
High-flow vascular malformations present difficult therapeutic problems. If high-flow malformations are quiescent, conservative management is appropriate. Arteriovenous malformations are rare in comparison with hemangiomas and venous malformations, and the experience of most surgeons is limited. Incomplete resection of
the nidus results in collateral formation and recurrence of the lesion. Poor surgical planning can lead to major bleeding and improper surgical ligation of major vessels.

Embolization should be the first choice of treatment for high-flow malformations (Dubois and Garel 2002). Embolization of the AVM can also be used as an adjunct to surgery (Persky 1986, Jackson et al. 1992, Kohout et al. 1998, Werner et al. 2001, Blei 2002); preoperative embolization reduces intraoperative blood loss and decreases surgical morbidity and mortality (Dean et al. 1994, Han et al. 1999). New techniques with developed endovascular treatment devices and new embolic agents have made embolization the treatment of choice for high-flow lesions. Catheterization of feeding arteries close to the nidus is possible with advanced microcatheters and injection of the embolic agent with a microcatheter wedged into the nidus may lead to permanent devascularization of the lesion without recurrence formation. Direct puncture embolization of AVM with N-butyl cyanoacrylate (NBCA) with good outcome has also been reported. This may be effective and safe, especially for superficial lesions (Han et al. 1999).

Materials used for embolization include liquid agents NBCA and absolute ethanol as well as mechanical devices like coils and particles (Lasjaunias and Berenstein 1987, Yakes 1996, Han et al. 1999, Dubois and Garel 2002). The new liquid embolic material ethylene vinyl alcohol copolymer (Onyx®) has been reported to be effective for treating intracranial high-flow malformations (Jahan et al. 2001, Florio et al. 2003), and there is at least one report about its use in peripheral embolizations (Castaneda et al. 2002).

2.6. Quality of life

A coherent classification system for quality of life assists in decision-making at the level of an individual patient. Apart from pathology based measures a quality of life assessment must cover both the functional and psychological effects of the disorder.

The most popular and extensively validated generic self-report measure is the SF-36 (Aaronson et al. 1992, Brazier et al. 1992, Garratt et al. 1993, Hays et al. 1993, McHorney et al. 1993, Jenkinson et al. 1994, Lyons et al. 1994, McHorney et al. 1994). SF-36 was designed for use in clinical practice and research, health policy evaluations and general population surveys. The SF-36 consists of 36 items and provides information on eight health domains: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions (Ware and Sherbourne 1992).
The RAND 36-Item Health Survey 1.0 (RAND-36), contains the 36 multiple-choice questions of the Medical Outcomes Study SF-36 “Short Form”. The recommended score algorithm is somewhat different from that of the SF-36 (Bell and Kahn 1996, Hays et al. 1993).

The Finnish version of the RAND-36 was presented in 1995 (Aalto et al.). Population reference values for the Finnish version of the RAND-36 have also been provided (Aalto et al. 1999).

There are also other indicators for quality of life like SIP, that provides an assessment of the consequences of the disorder on mobility, sleep and restriction in leisure activities (Bergner et al. 1981).

The Chronic Venous Insufficiency Questionnaire (CIVIQ) was developed to measure the quality of life of patients suffering from chronic lower limb venous insufficiency, in whom quality of life may be considerably impaired. Previous instruments measuring quality of life, like SF-36 and SIP, could not completely identify their specific complaints. CIVIQ is a self-administered questionnaire, exploring four dimensions of life: psychological, physical and social functioning and pain. It consists of a total of 20 equally weighted items. The scores used in CIVIQ are converted into an index, analogous to the index used to score the SF-36 (Launois et al. 1996).

2.7. Cost analysis

2.7.1. Costs of an interventional unit
Interventional radiology has greatly increased in the course of the last 20 years. Various new endovascular technique have been developed, such as vascular embolizations with GDC coils (Guglielmi Detachable Coils) and revascularizations (stent placement, stent grafts for aorta aneurysms). These new tools have brought new treatment options for diseases which formerly could only be treated by open surgical procedures. Intracranial aneurysms and aortic aneurysms are now often treated by endovascular technique. On the other hand this has added to the burden and expenses of the radiological units. The health care organizations and policy makers are increasingly concerned about the costs of health care. This is evidenced by many cost-benefit and cost-effectiveness analyses appearing in the medical care literature (Elixhauser et al. 1993, Friede et al. 1993, Lääperi 1996, Blackmore 2000). However, analyses dealing with angiography and interventional radiology have rarely been published, though radiological interventions have increased in number and technique. Radiological cost analyses are usually done with a conventional cost accounting method. With this method, the costs of specific expenses or purchases (e.g. x-ray film, salaries, billing company fees, travel expenses etc) are evaluated, and these expenditures are placed in “buckets”. However, this system suffers from an inability to report product or activity costs to a reasonable level of accuracy (Cooper 1990).
Conventional costing overcosts high-volume products and undercosts low-volume products, thus giving a false picture of the relations between production and costs (Ames and Hlavacek 1990).

2.7.2. Activity based cost (ABC) analysis
ABC accounting was originally designed for use in industry and service producing units (Kaplan and Cooper 1998). It has also been found appropriate for analysing the service units of health care (Roberts et al. 1999). ABC analysis is based on the assumption that activity creates costs, unlike in conventional accounting, where the products create the costs. When using ABC accounting, indirect costs especially are allocated to products more accurately than in conventional accounting. Besides identifying the cost factors, it is possible to analyse them in the different activities.

The costs are divided into direct and indirect costs. Direct costs are traceable to the performance of an intervention and they are divided into fixed and variable costs. Salaries of the regular personnel and depreciation are examples of fixed costs. When activity increases they remain unchanged up to a certain limit, until the activity increases so much that the capacity is not enough and more investments are needed. Variable costs like materials, drug and contrast media costs follow the activity changes. The fixed costs are considerable in health care. The principles of ABC are summarized in Fig 1.

Fig. 1. Principles of Activity Based Cost Accounting. The costs of the resources are collected into resource pools. The intervention is divided into activities to which the costs of resource pools are allocated according to cost drivers. The activity costs are allocated to products using activity drivers. Several resource pools can be utilized for an activity, and an activity can be divided into several products.
Activity based cost analysis has been used in many service organizations and achieved great benefits (Kaplan and Cooper 1998) when planning activity and budget, because the costs can then be more precisely allocated to their resources and the activity itself can be analyzed. In recent years interesting articles have been published on the costs in radiology using ABC accounting (Alanen et al. 1998, Laurila et al. 2000, Alanen et al. 2004), but comprehensive ABC analysis in an interventional radiologic unit is very few. In order to introduce a new method of treatment both cost-benefit and cost-effectiveness analyses should be done, but these are reliable only if they are preceded by an acceptable cost identification.

Optimal utilization and economic evaluation of limited health-care resources is needed and should be based on reliable cost accounting. The articles published so far concerning cost and cost-benefits consist of large variance concerning information on how the costs are created. Adams and Roub (1984) wrote an article on cost-effectiveness in outpatient angiography and interventional radiology. The authors do not describe how they collected the costs; only the amounts of assumed money to be saved is mentioned. Saini et al. (2000) compared the technical cost of radiological examinations. A major limitation of their study was that the cost of physician services and hospital overhead costs were not included.
3. AIMS OF THE PRESENT STUDY

1. To evaluate the clinical and radiological results of endovascular treatment for peripheral low-flow vascular malformations.

2. To determine the clinical and radiological pre-treatment findings affecting the endovascular treatment results.

3. To evaluate the costs of endovascular treatment for peripheral low-flow malformations from the viewpoint of the interventional unit.
4. MATERIAL AND METHODS

4.1. Patients

Tampere University Hospital has a catchment area of 1.15 million people. Between 1991 and 2001, 78 patients were treated endovascularly for peripheral vascular malformation at the Interventional Radiology Unit (Table 3). Fifty-eight of these patients met the inclusion criteria for the present study; 44 patients with venous malformations and 14 patients with lymphatic malformations compose the present study population. Six patients with venous malformations were not included in the present study because of their short follow-up time (less than one year from the last treatment session). Anatomic distribution of the lesions is given in Table 4. The median age of patients with venous malformations at the beginning of treatment was 22 years (range two months – 58 years; lower quartile 11 years, upper quartile 35 years). The median age for patients with lymphatic malformations was 5 years (range 10 months - 42 years; lower quartile 2 years, upper quartile 12 years). Twenty of the patients with venous malformations were younger than 16 years of age at the time of endovascular treatment and 24 patients were ≥16 years. Twelve patients with lymphatic malformations were under 16 and two patients were ≥16 years of age at the time of endovascular treatment.

<table>
<thead>
<tr>
<th>Malformations</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVMs and AV fistulae</td>
<td>14</td>
</tr>
<tr>
<td>Venous malformations</td>
<td>50</td>
</tr>
<tr>
<td>Lymphangiomas</td>
<td>14</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>78</td>
</tr>
</tbody>
</table>

*Table 3. Endovascularly treated peripheral malformations 1991-2001 at Tampere University Hospital.*

<table>
<thead>
<tr>
<th>Locations</th>
<th>Venous</th>
<th>Lymphangiomas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>female</td>
<td>male</td>
</tr>
<tr>
<td>Face or neck</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Upper extremity</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Lower extremity</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Trunk</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Generalized</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>25</td>
<td>19</td>
</tr>
</tbody>
</table>

*Table 4. Anatomic distribution of lesions in patients in present study.*
4.1.1. Patients in Studies I and II
The inclusion criteria for the study population included in study group I were: patients had undergone endovascular treatment for their low-flow extremity vascular malformation, the endovascular treatment was considered to be complete and at least one year had elapsed since the last treatment session. Twenty-four patients fulfilled these criteria and were asked to attend a clinical control. The clinical status of the patients, effect of the endovascular treatment and quality of life were evaluated.

Twenty consecutive patients with venous and capillary-venous malformation of the face and neck who had been endovascularly treated were included in study group II. Patients were invited to a clinical visit and MR imaging. The clinical status of the patients, therapeutic effect of the endovascular treatment, and quality of life were evaluated.

Low-flow vascular malformations can be problematic to treat, and some patients had already gone through several treatment attempts. Data on the previous treatments is given in Table 5.

<table>
<thead>
<tr>
<th></th>
<th>Venous malformations</th>
<th>Lymphangiomas</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Face and neck</td>
<td>Extremities</td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>11</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Surgery</td>
<td>8</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>In addition to surgery</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>- laser therapy</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>- radiation therapy</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Endovascular</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Interferon</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Laser therapy</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Table 5. Other treatments before endovascular treatment.*

4.1.2. Patients in Studies III and IV
Between January 1999 and February 2001 OK-432 sclerotherapy was begun for 14 patients with lymphangioma. The initial treatment results were examined in Studies III and IV. No quality of life analysis was performed for patients with lymphatic malformations because 1) the median age at the time of the first injection was only 5 years and 6 months and 2) even though they are benign lesions treatment of symptom free lymphangiomas is justified due to the complications they may appear with.

4.1.3. Study V
The aim of Study V was to analyse the costs of catheter-based angiography and interventional radiological procedures using ABC (Activity Based Cost Analysis) and to identify the cost factors in the various activities. The study was carried out for the calendar year 1999, when the number of procedures in the Interventional Radiological Unit at
Tampere University Hospital was 2968; 1601 of these were diagnostic angiographies, 526 endovascular, and 841 nonvascular interventions. The results of Study V are utilized in the present study, especially in relation to the costs of the endovascular treatment of low-flow malformations.

4.2. Treatment indications

All of the patients with venous malformations had presented with symptoms due to the malformation (Table 6). No purely cosmetically upsetting malformations were treated. Patients with venous malformations in the extremities had swelling and pain as dominant symptoms, and patients with malformations in the face and neck had swelling and cosmetic disturbances as dominant symptoms and signs.

Treatment of lymphangiomas is generally justified even though they are benign lesions, because of the potential complications they may be related to. The decisive clinical sign among patients with lymphangiomas was swelling (Table 6).

<table>
<thead>
<tr>
<th>Symptoms and signs</th>
<th>Venous malformations</th>
<th>Lymphangiomas</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Face and neck (20 pts)</td>
<td>Extremities (24 pts)</td>
<td>(14 pts)</td>
</tr>
<tr>
<td>Swelling</td>
<td>19</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Pain</td>
<td>5</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Cosmetic disturbances</td>
<td>9</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Inhibited function</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>No symptoms</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 6. Symptoms and signs before endovascular treatment in patients with low-flow malformations.

4.3. Clinical and radiological investigations

Patients with venous malformations had been clinically investigated by a specialist in vascular surgery or otolaryngology. All the patients with lymphatic malformations were referred to endovascular treatment from the otolaryngological department.

The data concerning patients’ medical history and physical examinations before and after endovascular treatment, as well as the data concerning the endovascular treatment, was collected from the patient files.

Prior to endovascular treatment the clinical diagnosis had been confirmed by radiological imaging: angiography, magnetic resonance imaging (MRI), computed tomography or a combination of these modalities. The information on various pre-treatment imaging modalities is given in Table 7. All the pre-treatment radiological examinations were
analyzed by the researchers. Before endovascular therapy was started, all lesions were also evaluated by ultrasonography. The radiological inclusion criteria for the venous malformations was that no arterial components in the lesions appeared in the pre-treatment imaging. The lymphatic lesions were classified as macrocystic (diameter of the cysts greater than 2 cm), microcystic (less than 2 cm), or mixed.

### 4.4. Endovascular treatment procedure

The aim of the treatment was to free the patient of his/her symptoms. The treatment was continued until this was achieved, or until the patient was satisfied with the remaining symptoms (choice between the side-effects of the therapy and remaining symptoms). The interval between each treatment session was planned to be between one and two months. This time is long enough to let the swelling and changes directly related to sclerotherapy subside so that the proper clinical status can be evaluated. All the patients in the present study had primarily low-flow malformations, which were treated by endovascular sclerotherapy. Some patients had more complex vascular malformations, and these were treated by other endovascular techniques. Embolizations with PVA particles and GDC coils were performed with transarterial microcatheter technique. A detailed list of various endovascular procedures for venous and capillary-venous malformations is given in Table 8.

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Venous malformations</th>
<th>Lymphangiomas</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Face and neck</td>
<td>Extremities</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Ultrasonography</td>
<td>20</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>Catheter Angiography</td>
<td>20</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Magnetic Resonance Imaging</td>
<td>7</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Computed Tomography</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 7. Imaging modalities before endovascular treatments.

### Table 8. Endovascular treatments of venous and capillary-venous malformations.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Face and neck (20 pts)</th>
<th>Extremities (24 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sclerotherapy with ethanol</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>In addition to ethanol injections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- embolization of a capillary component with PVA particles</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>- embolization of a small AV fistula with GDC coils</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>- aethoxysclerol injection</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>- therapy of lymphangioma with OK-432 injection</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Embolization of capillary-venous malformation with PVA particles</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Table 8. Endovascular treatments of venous and capillary-venous malformations.
4.4.1. Sclerotherapy, venous malformations
The malformation was punctured under ultrasound and fluoroscopy guidance. Superficial lesions were punctured with a 23 G butterfly needle and the deeper lesions were punctured with a 20 G needle, which was attached to a connecting tube (length 20 cm). The position of the needle was checked by aspiration. Direct puncture flebography with DSA technique was performed to verify the diagnosis and the needle placement in the lesion and to determine the volume before the draining veins were filled with contrast. The malformation was filled with 99.5 % ethanol to a volume of approximately 1/2-2/3 of that evaluated with contrast media. No contrast media was added to the ethanol. In the case of a large malformation, punctures of different compartments and injections were performed at the same session. The predetermined maximum volume 1ml/kg was never reached. Because of the pain occurring when ethanol is injected intravascularly, sclerotherapy was performed under general anesthesia, regional nerve block, or epidural or spinal anesthesia.

4.4.2. Sclerotherapy, lymphangiomas
The injections were mostly performed using ultrasound or fluoroscopic guidance. Some of the superficial injections were done after fluid aspiration, without any radiological guidance. The concentration of OK-432 was 0.01mg/ml (0.1 mg of OK-432 per 10 ml of physiological saline). After the needle was introduced into the cyst, contrast agent was injected to verify needle placement in the lesion, to image the possible communication of the intralesional spaces, and to determine the amount of OK-432 to be injected. The fluid was aspirated from the cystic space and the same volume of OK-432 solution was injected. If this was not possible, approximately half of the estimated volume was injected. If the intralesional spaces did not communicate in the previous contrast injection, OK-432 was injected at several sites. The maximum volume injected at one treatment session was 10 ml. The treatment of children was performed under general anesthesia, for adults only local anesthesia was needed.

4.5. Analysis of the treatment results

4.5.1. Clinical visit
One vascular surgeon experienced in venous diseases performed all the clinical examinations for the patients in Study I, and one specialist in otolaryngology experienced in vascular anomalies performed all the clinical examinations for the patients in Study II. The symptoms related to the remaining vascular malformation were divided into four groups: no symptoms, slight, moderate and severe symptoms. The clinical status included the following items in the previously treated region: palpation (palpable masses, pain), inspection (skin changes, mucous discoloration) and auscultation (possible shunting). The affected area was observed by recording peripheral arterial pulses, varicose veins, oedema and skin condition.
One specialist in otolaryngology experienced in vascular anomalies performed all the clinical examinations for the patients in Studies III and IV.

4.5.2. Quality of life
At the same clinical visit the patients in Studies I and II independently completed a questionnaire measuring quality of life to evaluate the patients’ subjective opinion concerning their state of health after treatment. The questionnaire included 20 multiple-choice questions, equally weighted, and exploring four dimensions: psychological, physical and social functioning and pain (Appendix, English version of the questions). Adding scores for each constituent item yielded the score for each dimension and the total score was obtained by summing the 20 items. Absolute scores were converted into an index. The value of the indices is directly proportional to the degree of deterioration of quality of life: 0 representing the highest quality of life and 100 the lowest. Those patients who did not attend the clinical examination were asked to complete the same multiple-choice questionnaire.

4.5.3. Radiological examinations
In order to obtain a coherent impression of the significance of MR imaging as a follow-up study, all the patients in study group II (face and neck venous malformations) were invited to attend for MR imaging. One patient did not attend the MRI study. T1-weighted images were obtained in one plane and T2-weighted fat saturated images in two planes. No contrast media was used, because the aim was to ascertain the possible remaining extent of the venous malformation.

The response to treatment in study groups I and III and IV had been analyzed as part of normal clinical follow-up using the same modality as prior to treatment, or with ultrasound imaging.

All the pre-treatment and post-treatment radiological examinations were reviewed by two radiologists together in consensus. The location, the extent and size of the malformation, likewise possible capillary components were evaluated from the images. Radiological result of the treatment was classified on a four grade scale: complete volume reduction, marked response (≥50% volume reduction), moderate response (<50% volume reduction), and no response.
**Appendix**

**Questionnaire for patients with venous malformations**

The following questions relate to a certain number of symptoms, sensations or discomforts that can make everyday life more or less difficult. For each symptom listed we ask you to answer the corresponding question in the following manner:

Please indicate whether you have experienced what is described in the sentence, and if so, to what intensity.

**The following questions are concerning the venous malformation**

1. If you have felt pain, what was the intensity of this pain?

<table>
<thead>
<tr>
<th>No pain</th>
<th>Light pain</th>
<th>Moderate pain</th>
<th>Strong pain</th>
<th>Intense pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

2. To what extent did you feel bothered/limited in your work or other daily activities because of your problem?

<table>
<thead>
<tr>
<th>No bothered/ limited</th>
<th>A little bothered/ limited</th>
<th>Moderately bothered/ limited</th>
<th>Very bothered/ limited</th>
<th>Extremely bothered/ limited</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

3. Have you slept badly because of your problems, and how often?

<table>
<thead>
<tr>
<th>Never</th>
<th>Seldom</th>
<th>Fairly often</th>
<th>Very often</th>
<th>Every night</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

To what extent did your problems bother/limit you while doing the movements or activities listed below?

<table>
<thead>
<tr>
<th>Not bothered/ limited at all</th>
<th>A little bothered/ limited</th>
<th>Moderately bothered/ limited</th>
<th>Very bothered/ limited</th>
<th>Impossible to do</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

4. Standing for a long time

5. Climbing stairs

6. Crouching, kneeling

7. Walking briskly

8. Travel by car, bus, plane

9. Housework such as working in the kitchen, carrying a child, cleaning floors, doing handy work, ironing

10. Going to discos, weddings, parties

| 1 | 2 | 3 | 4 | 5 |
Problems can also have an effect on one’s morale. To what extent do the following sentences correspond to the way you have felt?

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Not at all</th>
<th>A little</th>
<th>Moderately</th>
<th>A lot</th>
<th>Absolutely</th>
</tr>
</thead>
<tbody>
<tr>
<td>11. Sporting activities</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>I feel myself nervous</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>13</td>
<td>I become tired quickly</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>14</td>
<td>I feel I am a burden to people</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>15</td>
<td>I must always be careful with my extremity</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>16</td>
<td>I am embarrassed to show my extremity</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>17</td>
<td>I get irritated easily</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>18</td>
<td>I feel handicapped</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>19</td>
<td>I do not feel like going out</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>20</td>
<td>I feel myself depressive</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
4.6. Cost analysis for interventional radiology unit

All costs (in Euros, €), directly related to activities in interventional radiology were accounted from the perspective of the interventional unit. The overhead costs for the hospital and the radiological unit were not included. They were only about 5% of the total budget. Patient premedication, general anesthesia and care on the ward before and after the procedure were not included, because these costs were directly charged from the budgets of the wards.

The information concerning cost and consumption was acquired from the hospital accounting department and from inventory files. The costs of the resources were divided into four main categories; personnel, equipment, premises and materials. Personnel costs consisted of salaries (including taxes and social security contributions) and educational expenses. The educational expenses were 1% of the payroll. Equipment costs consisted of investments, maintenance and updating costs. Premise costs consisted of capital investments and running costs like electricity, water, cleaning and furnishing. Because storage space was limited, the material was purchased at the same rate as it was used, so material costs consisted of the material actually used.

The costs were analyzed using Activity Based Cost Analysis (Ecomed/IC Digital Equipment Corporation, Helsinki, Finland). All activities required in the production of catheter-based angiographies and interventions were identified separately. There were altogether 34 different activities that were divided into five main categories: main procedure, preparation of intervention and patient, aftercare of patient, information on the intervention and clinical meeting. The process model was defined for each product line. Resource pools and cost drivers were identified for each activity.

Costs of resources were collected into 30 resource pools, each of which contained functionally or spatially related resources. For example, the costs of the biplane c-arm angiography system and the rent of its room were allocated to the resource pool “angiosuite 1” and the pool “microcathetering kit” was formed from the costs of the microcatheters, microwires, connectors etc. The resources were allocated to pools according to their real use. Costs were allocated to activities according to resource use as expressed by cost drivers. For example, the costs of the pool “angiosuite 1” and the pool “microcathetering kits” were divided with the help of cost drivers into activities that utilize those pools like “embolizations with GDC coils, embolizations with glue” and so on. Cost drivers for personnel, equipment and premises were defined as the time required for the activity multiplied by the frequency of this activity, and for materials as the actual amount used. The number of personnel required was taken into account when allocating the personnel costs. The information on average time, number of personnel and materials required was collected from the logbook of the year 1999. The activity based costs were allocated to products in proportion to the numbers performed.
Acquisition costs of equipment were distributed over the period 1989-1999. The angiography equipment was purchased in 1989 and 1996. The total cost of both sets of equipment was 1.7 million €. The capital investment was depreciated in equal instalments. The amortization period of one angiography machine was 15 years, for an ultrasound scanner and a laser imager it was 8 years and for X-ray tubes 5 years, which corresponds to their real utilization time at Tampere University Hospital. Three cost comparisons were performed. In the baseline calculations the amortization period was set at 15 years and the interest rate for invested capital for angiography was defined as 4%. In addition, a sensitivity analysis was carried out, in which the amortization period for angiography equipment was set at 15 years and the interest rates at 0% and 8% respectively. In Finland the hospitals are largely community subsidized. This means all equipment to be purchased is paid for immediately, not loaned, so the interest rate of 0% was also analyzed. Finally the amortization period was set at 10 years and interest rate at 4%.

The invoice during the year 1999 for the interventional unit was obtained from the hospital book-keeping. These prices were based on previous traditional cost accounting. The revenues were compared to the costs accounted by ABC analysis.

4.7. Statistical analysis

The patients’ quality of life and its dimensions’ dependency on the following parameters were analysed: patient’s sex and age at the beginning of the endovascular treatment, anatomic location of the malformation, size and type (purely venous or capillary-venous), clinical findings before endovascular treatment, previous treatment, patient’s age at the clinical visit, clinical findings after follow-up, MR finding after follow-up for the patients with venous malformations in the face or neck, and how patient follow-up was organized.

The difference between the two sample means was tested with Student t test. The Mann-Whitney U test was used to compare the two populations with unequal variance. For categorical data, the Fisher exact test was used. The relationships between continuous variables were tested with correlation and simple linear regression analysis. Statistical analysis was performed using StatsDirect statistical software, version 2,3,2 (Cheshire, United Kingdom). A p-value less than 0.05 was considered to indicate a statistically significant difference.

4.8. Approval of the Ethics Committee

The study protocol was approved by the Ethics Committee of Tampere University Hospital and written informed consent was obtained from the patients or parents of young children.
5. RESULTS

5.1. Clinical findings

All the patients with venous malformations had presented with symptoms and signs due to their malformations (Table 6). The dominant clinical findings for the patients with venous malformations in the head and neck were swelling and cosmetic disturbances, and for the patients with venous malformations in the extremities the dominant findings were swelling and pain.

The main clinical finding among patients with lymphatic malformations was swelling. In addition, two patients suffered from dyspnoe due to the lesions that compressed the airways and one patient presented with exophthalmus due to her retrobulbar lesion.

5.2. Radiological findings

5.2.1. Venous malformations

The venous malformations were classified as large (>5 cm in maximum diameter) in seventeen patients and small in 27 patients. The lesions were classified as deep in 38 patients and six patients had a superficial lesion. The whole muscle or muscle compartment was filled by the malformation in five of the patients with malformations in the extremities. Capillary-venous malformations or a capillary component in the malformation was found in six of the 44 patients and one patient had a small AV fistula in addition to an extensive venous malformation. Both venous malformation (in the face and neck) and lymphangioma were found in one patient.

5.2.2. Lymphatic malformations

The lymphatic lesions were defined as large (>5 cm in maximum diameter) in twelve patients and small in two patients. The lesions were classified as macrocystic in nine of the patients and five patients had a mixed lesion. Skeletal involvement was found in one patient. Two had a combination of lymphangioma and some other vascular anomaly; one Klippel-Trenaunay syndrome, with a venolymphatic lesion in the upper extremity and one further patient with a combination of lymphangioma in the cervical region and macroglossia (capillary-venous malformation in the tongue).

5.3. Treatment results

5.3.1. Clinical visit

5.3.1.1. Venous malformations

The mean follow-up time from the first endovascular treatment session to the clinical control was 2 years and 10 months (range 1 year 3 months – 15 years 8 months). Based on the clinical study performed by a vascular surgeon or an otolaryngologist 10
(26%) patients had no clinical symptoms or signs related to the malformation at the clinical visit, 17 (45%) patients had slight, nine (24%) patients had moderate and two (5%) patients presented with severe symptoms or signs. No deterioration of the initial situation was noted. Six patients did not attend the clinical control. Their clinical status was assessed from the medical records from previous clinical visits. The major clinical findings were palpable mass (21 patients), swelling (14 patients) mucous discoloration (11 patients), skin changes (7 patients) and tenderness (4 patients).

5.3.1.2. Lymphangiomas
After a mean follow-up period of 1 year and 1 month after the first OK-432 injection no recurrences were discovered (range 3 months - 2 years and 3 months). In 13 (93%) patients symptoms or signs had disappeared (n=6) or improved (n=7). One patient with Klippel-Trenaunay syndrome showed no improvement from sclerotherapy, and his venolymphatic lesion in the upper extremity was surgically treated.

5.3.2. Quality of life
5.3.2.1. Patients with venous malformations
The quality of life analysis was evaluated from study groups I and II. The questionnaire was not returned by two patients. In the opinion of the patients three (7%) had no symptoms or signs, 26 (59%) patients had improvement in their symptoms and signs, 11 (25%) had unchanged symptoms or signs and four (9%) patients had first diminished symptoms, but the symptoms recurred later (Table 9).

<table>
<thead>
<tr>
<th>Patients' opinions</th>
<th>Malformation in face or neck</th>
<th>Malformation in extremities</th>
<th>Lymphangiomas</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete cure</td>
<td>1</td>
<td>2</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Improvement</td>
<td>10</td>
<td>16</td>
<td>5</td>
<td>31</td>
</tr>
<tr>
<td>No improvement</td>
<td>7</td>
<td>4</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>First improvement then recurrence</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>24</td>
<td>14</td>
<td>58</td>
</tr>
</tbody>
</table>

Table 9. Patient's subjective grading of treatment effect.

The results concerning quality of life showed that most patients did well after endovascular treatment. The overall results of the quality of life analysis is given in Table 10. Pain was the most important injurious factor for state of health (p< 0.05) when all venous malformations were analyzed together. In the malformations involving the extremities (n=23) pain accounted for more deleterious affect on quality of life than among patients with malformations involving the face and neck (n=19) (extremities: mean of pain 28.8, SD 22.7, range 0-81; face and neck: mean of pain 15.5, SD 14.2, range 0-38, p=0.03). For the other three dimensions there were no statistically significant differences between study groups I and II.
Those patients younger than 16 years at the beginning of the treatment (n=20) had better quality of life (mean 10.3, SD 11.8, range 1-52) than patients 16 years or older (mean 21.4, SD 16.9, range 0-74, p=0.02) (Fig 2). The greatest difference between indices was found for the psychological dimension when comparing the results of these two age groups (p=0.02).

There was a positive correlation between deterioration in quality of life and patients’ age at the beginning of the treatment (r=0.35, r² = 0.12, p=0.02). When correlation between deterioration of quality of life and patient’s age at the beginning of the treatment was studied separately for malformations in the extremities and malformations in the face and neck, a moderately positive correlation was found for patients with malformations in the face and neck (r= 0.62, r² = 0.38, p= 0.01) (Fig 3) and no significant correlation found separately for patients with malformations in the extremities (r=0.20, r²=0.04, p=0.40). Other variables tested, including possible surgical treatment before endovascular therapy, were not statistically significant.

5.3.2.2. Special characteristics for venous malformations in the extremities
The poorest outcome was found among patients whose malformation at the clinical control caused swelling of the affected extremity (mean 40.3, SD 26.5, range 20 – 79). The difference was statistically significant (p= 0.01). The patients whose malformations filled the whole muscle or muscle compartment had poorer quality indices (p=0.04) than others (mean 34.6, SD 26.3, range 10 – 79) and perhaps also those in whom the maximum diameter of the lesion was 5 cm or more (p=0.05). The other variables tested were not statistically significant. The tested variables and results are given in Table 11.
Fig. 2. Dimensions of the deterioration of life quality compared to patients’ age at the beginning of endovascular treatment.

Fig. 3. Deterioration of life quality correlated to the patients’ age at beginning of endovascular treatment; patients with venous malformations in the face and neck. ($r = 0.62$, $r^2 = 0.38$, $p = 0.01$)
<table>
<thead>
<tr>
<th>Nr of pts</th>
<th>Quality index</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>female</td>
<td>13</td>
<td>24.2</td>
<td>21.4</td>
<td>3</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>male</td>
<td>10</td>
<td>13.0</td>
<td>10.1</td>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td>Location of malformations</td>
<td>upper extremities</td>
<td>10</td>
<td>14.2</td>
<td>11.0</td>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>lower extremities</td>
<td>13</td>
<td>23.2</td>
<td>21.6</td>
<td>5</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>deep</td>
<td>20</td>
<td>20.1</td>
<td>18.8</td>
<td>3</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>superficial</td>
<td>3</td>
<td>14.3</td>
<td>12.6</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>no pararticular</td>
<td>12</td>
<td>18.2</td>
<td>14.7</td>
<td>1</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>pararticular</td>
<td>11</td>
<td>20.5</td>
<td>21.8</td>
<td>5</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>muscle compartment partially filled with malformation</td>
<td>18</td>
<td>15.1</td>
<td>13.0</td>
<td>1</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>muscle compartment totally filled with malformation</td>
<td>5</td>
<td>34.6</td>
<td>26.3</td>
<td>10</td>
<td>79</td>
</tr>
<tr>
<td>Size (max. diameter)</td>
<td>&lt; 5 cm</td>
<td>10</td>
<td>11.7</td>
<td>8.1</td>
<td>3</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>≥ 5 cm</td>
<td>13</td>
<td>25.1</td>
<td>21.4</td>
<td>1</td>
<td>79</td>
</tr>
<tr>
<td>Patients' age at first treatment</td>
<td>younger than 16 years</td>
<td>11</td>
<td>14.2</td>
<td>14.7</td>
<td>3</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>16 years or older</td>
<td>12</td>
<td>24.0</td>
<td>20.0</td>
<td>1</td>
<td>79</td>
</tr>
<tr>
<td>Palpation findings after follow up time</td>
<td>mass</td>
<td>12</td>
<td>20.9</td>
<td>21.1</td>
<td>1</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>no mass</td>
<td>7</td>
<td>16.6</td>
<td>10.2</td>
<td>3</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>tenderness</td>
<td>4</td>
<td>22.2</td>
<td>6.7</td>
<td>14</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>no tenderness</td>
<td>15</td>
<td>18.5</td>
<td>19.7</td>
<td>1</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>no swelling</td>
<td>15</td>
<td>13.7</td>
<td>9.6</td>
<td>1</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>swelling</td>
<td>4</td>
<td>40.3</td>
<td>26.5</td>
<td>20</td>
<td>79</td>
</tr>
</tbody>
</table>

Table 11. Quality of life in different groups in patients with venous malformations in extremities.

5.3.2.3. Special characteristics for venous malformations in the face and neck

Those patients (n=9) who were under 16 years at the beginning of the treatment had better quality of life than patients 16 or older (indices mean 6.1, SD 4.1 vs mean 20.1, SD 14.9, p=0.02). Patients (n=5) with venous malformations of the tongue had worse outcome than others (indices mean 24.8, SD 18.9 vs mean 9.5, SD 7.8, p=0.04). Patients (n=4) who had a capillary component in their venous malformation (indices mean 3.4, SD 2.8 vs mean 17.1, SD 13.4, p=0.01) had better quality of life. Those patients (n=13) remaining in clinical control under physicians specialized in vascular malformations after the endovascular treatment had better quality of life (indices mean 7.8, SD 6.0 vs mean 21.3, SD 16.3, p=0.04). Other variables tested were not statistically significant. The tested variables and results are given in Table 12.

5.3.3. Radiological findings

The results of a comparison between pre-treatment imaging and post-treatment MR imaging (19 patients) were as follows: Reduction in size was marked in eight patients, moderate in three patients and nil in eight patients. No additional venous malformations were discovered in post MR imaging.
Table 12. Quality of life in different groups of patients with venous malformations in face and neck.

Volume reduction of venous malformations did not correlate significantly with the deterioration in quality of life (Spearman rank correlation coefficient = 0.35, p = 0.15).

Complete or marked reduction in volume was achieved in eleven patients with lymphatic lesions (79 %), with complete reduction dominating among patients with a macrocystic lesion (5 out of 9 i.e. 56 %), and marked reduction among mixed lesions (3 out of 5 i.e. 60 %).

5.4. Clinical and radiological findings associated with treatment results

In venous malformations the anatomic location of the lesion, size, composition (purely venous or with a capillary component), possible previous surgical treatment and patient’s age at the beginning of the endovascular therapy (<16 or ≥16) were compared to the treatment results (patient’s opinion of the treatment results). No statistically significant determinants were found.

In lymphangiomas the favourable results among patients with macrocystic lesions were obtained with fewer sessions and with smaller amounts of OK-432, than among those with mixed lesions. All patients who received OK-432 as first line treatment had complete or marked response. After surgery or interferon therapy the results were not so favourable, in spite of a greater number of sessions and larger volumes of OK-432 (Table 13). These results were statistically significant (p< 0.05).
5.5. Complications

The major complication rate for the whole study population was 6.9 % (4/58). However, all these four patients recovered. One patient who received ethanol sclerotherapy for facial venous malformation suffered a transient facial paresis. One patient receiving sclerotherapy for venous malformation in the elbow presented with a transient slight paresis of the radial nerve. Another patient had skin necrosis of 1 cm diameter in his hypothenar, which healed with local wound care. Most patients demonstrated focal swelling and pain in the area treated for 1-2 weeks, which was accepted as a normal reaction to the induced thrombosis.

Among the patients with lymphatic malformations slightly elevated temperature in the first few days after injection was recorded in 11 patients. This is an expected reaction to a successful injection. One patient developed an intense cervical swelling after the first injection. No other complications were encountered.

5.6. Further treatment

In five of the 44 patients with venous malformations surgical excision was performed after sclerotherapy; one patient had the lesion on the tip of the nose and three patients had venous malformation of the lips. One patient had her pronator teres muscle infiltrated with malformation, and this was resected with poor subjective result.

Two out of 24 patients with malformations in the extremities first had diminished symptoms, but the symptoms recurred later. Of these two one had a recurrence during puberty and the other during pregnancy. The latter with treated malformation in her thigh was subsequently discovered to have a high-flow vascular malformation in her ankle. This was treated endovascularly by transcatheter embolization with glue and PVA particles. Two patients with malformations in the face and neck also had good treatment results but the symptoms came back during puberty and one had a mixed veno-lymphatic malformation, and the lymphatic component had not been treated.

<table>
<thead>
<tr>
<th>Lymphangiomas</th>
<th>Mean size (cm)</th>
<th>Mean no of sessions</th>
<th>Mean total doses of OK-432 (ml; 0.01 mg/ml)</th>
<th>Volume reduction</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td></td>
<td></td>
<td></td>
<td>&gt; 50 % &lt; 50 %</td>
<td></td>
</tr>
<tr>
<td>macrocystic</td>
<td>8.6</td>
<td>1.7</td>
<td>12.1</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>mixed</td>
<td>6.8</td>
<td>3.2</td>
<td>20.5</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Earlier treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>8.1</td>
<td>1.6</td>
<td>10.3</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>surgery</td>
<td>8.2</td>
<td>2.8</td>
<td>23.6</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>interferon</td>
<td>5.0</td>
<td>4.0</td>
<td>11.1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 13. Volume reduction in correlation with type and earlier treatment of lymphangiomas.
Two out of 14 patients with lymphatic malformations were treated surgically after OK-432 therapy. One patient had macrocystic lymphangioma in the submandibular area. She had already been treated surgically before OK-432 injections. After two OK-432 injections her lesion showed only a moderate regression. Thereafter she was treated surgically but for the time being there is recurrence of the lesion and a new surgical treatment is being planned. The other patient had Klippel-Trenaunay syndrome, and his venolymphatic lesion in the upper extremity was surgically treated. In this operation the venous component was moderately reduced in size. One of the patients had a combination of lymphangioma in the cervical region and macroglossia (capillary-venous malformation in the tongue). The latter was treated with repeated transcatheter embolizations.

5.7. Cost of interventional radiological unit

In 1999 the budget of the interventional unit was 1 844 416 €. Material costs accounted for 67% (1 252 070 €), personnel costs for 17% (309 466 €), equipment costs for 14% (254 624 €) and premises costs for 2% (28 256 €) of this. Diagnostic catheter-based angiographies accounted for 34%, embolizations and vascular sclerotherapies accounted for 35%, revascularizations accounted for 17% and nonvascular interventions 14% of the costs. The most expensive products in the endovascular interventions were embolizations of cerebral aneurysms (4 472 €) and AVMs (3 082 €) and stent-graft placement of aortic aneurysms (5 291 €). Biliary stenting was the most expensive product of the nonvascular interventions (1 374 €).

Cost categories in the main activities are graphically illustrated in Fig 4. In the group “embolizations and endovascular sclerotherapies” material costs formed 92% and in “revascularizations” 87% of the total costs of the main procedure. In other intervention types it was 54-64%.

![Fig 4. Cost categories in main activities (€), graphically illustrated.](image)
5.8. Cost of low-flow malformation treatment

Costs of the various activities of all peripheral microcatheter embolizations and direct puncture sclerotherapies are given in Table 14. The main procedure accounted for 96% of the costs in embolizations with microcatheter technique, while it accounted for 70% of the costs in sclerotherapies. The distribution of cost categories in the main activities is graphically illustrated for embolizations with microcatheter technique in Fig 5 and in Fig 6 for sclerotherapies. The material costs form a remarkably greater part of the main activity in microcatheter embolizations compared to sclerotherapies. Microcatheter kits form the most expensive part of the material costs in embolizations with microcatheter technique. The mean cost of one embolization session with microcatheter technique was 1820 €, and 231 € for a sclerotherapy of venous malformation or lymphangioma.

<table>
<thead>
<tr>
<th>Activities</th>
<th>Microcatheter embolizations (N=61)</th>
<th>Sclerotherapies of venous malformations and lymphangiomas (N=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>€</td>
<td>%</td>
</tr>
<tr>
<td>Main activity</td>
<td>106839</td>
<td>96.2%</td>
</tr>
<tr>
<td>Preparation of intervention and patient</td>
<td>2089</td>
<td>1.9%</td>
</tr>
<tr>
<td>Aftercare of patient</td>
<td>1392</td>
<td>1.3%</td>
</tr>
<tr>
<td>Information of intervention</td>
<td>472</td>
<td>0.4%</td>
</tr>
<tr>
<td>Clinical meetings</td>
<td>210</td>
<td>0.2%</td>
</tr>
<tr>
<td>Total</td>
<td>111002</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 14. Costs of the activities in the treatment of vascular malformations.
Fig 5. Distribution of cost categories in the main activity of embolizations for embolization with microcatheter technique.

Fig 6. Distribution of cost categories in main activities in sclerotherapies.
6. DISCUSSION

6.1 Patient selection

In order to select patients for endovascular treatment it is essential to distinguish between vascular malformations and hemangiomas. In most instances the diagnosis of hemangioma can be made on the basis of the history and clinical examination (Fishman and Mulliken 1998). MRI is the best imaging method in diagnosing low-flow malformations. Sporadically low-flow malformations may contain high-flow components, like one patient in Study I with a small arteriovenous fistula. Possible small high-flow components may be complicated to discover from MR images even for the most experienced radiologist; they are best visualized in DSA. The other imaging method to detect high-flow components is ultrasound, which was also used in the present study for all lesions before endovascular therapy.

The main locations for venous malformations are the head and neck (40%), the extremities (40%) and the trunk (20%) (Dubois and Garel 1999). Between 1991 and 2001, 50 patients were treated endovascularly for peripheral venous malformation at the Interventional Radiology Unit. Six patients out of these 50 patients did not meet the inclusion criteria for the present study due to ongoing endovascular treatment. The patients with peripheral venous malformations in the present study represent the general distribution of peripheral venous malformations and the results of this study can be compared with those previously reported.

All 14 patients with lymphatic malformations treated with OK-432 sclerotherapy during this time were included in this study, and the treatment results of this study population are also comparable to previous reports.

6.2. Treatment results; venous malformations

The treatment results in the present study concur with the previous reports concerning endovascular treatment of venous malformations. Based on the clinical examination, after endovascular treatment 95% of the patients in Studies I and II had improved symptoms or signs. The results from previous reports are 59-100 % (Table 1). The possible variables that might influence the results, however, have seldom been reported. Most often the reports focus on the final results of sclerotherapy. This, in a way, supports our conclusion of not finding any major statistically significant clinical or radiological factor affecting the treatment results when comparing various clinical and radiological findings before treatment to corresponding variables after treatment.
Occasionally surgical intervention is needed after endovascular treatment. The main indication for surgery after endovascular treatment for venous malformations is cosmetic correction.

6.2.1. Quality of life after treatment

In the present study the treatment results of venous malformations were also analyzed using a questionnaire that covered the patients’ quality of life after treatment. In general, the results concerning quality of life showed that most patients did well after endovascular treatment. The numbers of total quality were equal compared to aged matched Finnish normal population (Aalto et al. 1999). This evaluation revealed several significant prognostic factors concerning endovascular treatment results of venous malformations. Clinical examination or patients’ s opinion did not reveal these factors. Those patients < 16 years at the beginning of the treatment had better quality of life than patients 16 years or older at the beginning of treatment. When this result was analyzed in even more detail, the quality of life was better especially among patients with venous malformations of the face and neck. This supports beginning the endovascular treatment before puberty, particularly when the malformations is located in the face or neck, to achieve better treatment results and to avoid problems later on.

In everyday practice the aim of the treatment is to make the patient symptom free. The treatment is continued until this is achieved, or until the patient is satisfied with the remaining symptoms. In this study the quality of life analysis showed that patients whose malformation at the clinical control caused swelling to the extremity affected had poorer quality indices than others. This emphasizes the importance of clinical follow-up and decision-making, about which lesions to treat further, even though the initial treatment results satisfied both the patient and the clinician.

Patients with venous malformations of the tongue had poorer outcome than others. Although improvement in symptoms and malformation size was seen in some of these patients, their quality of life was significantly poorer after treatment compared to others. This is probably due to the fact that complete obliteration of the malformation is seldom achieved, and even small residual malformation in the tongue may impede speech and swallowing. Though the major method of follow-up is clinical control, in certain cases such as these patients with malformations of the tongue, radiological imaging will be needed during follow-up.

When analysing the pre-treatment imaging and quality of life results, the poorest outcome was found in malformations that filled the whole muscle or muscle compartment and in larger lesions. In addition it was found that lesions in the lower extremities had poorer long-term results compared to lesions in the upper extremities. These findings are to be expected, because lesions in the lower extremities do bring about more symptoms due to hydrostatic pressure, and lesions covering the whole muscle or muscle compartment are
larger in volume and so bring about more swelling. Patients who had a capillary component in their venous malformation had better quality of life. These factors may have a prognostic value and have to be taken into account when planning the treatment. This moreover underlines the importance of appropriate radiological imaging before endovascular treatment.

From the results of this study it may be concluded that clinical control performed under physicians specialized in vascular malformations is the most appropriate method of follow-up. Those patients who remained in clinical control by physicians specialized in vascular malformations after the endovascular treatment had better quality of life. This is obviously due to the fact that vascular malformations are rare in incidence, and general practitioners lack adequate experience and information concerning their treatment and follow-up.

In the present study it was found that the questionnaire on quality of life evaluated patients’ state of health more accurately than pure subjective opinion. This quality of life analysis included 20 multiple-choice questions, and is easy and fast to administer in conjunction with the clinical control after endovascular treatment. It would probably also be useful in pre-treatment evaluation to better understand the degree of symptoms and signs related to the malformation, also when considering possible further treatment, it might be valuable. On the basis of this study it seems warranted to use the questionnaire in everyday practice, in order to achieve the best attainable treatment results for individual patients.

Imaging control, especially MR imaging, is valuable in certain cases, such as in lesions involving face and neck where small residual malformations not clinically apparent may cause significant problems. In cases where the condition does not improve despite ongoing treatment one should also confirm the diagnosis of malformation with new imaging. Mixed lesions are possible and high-flow components may maintain the condition, as also discovered in one of our patients. In cases of ongoing treatment of a large malformation MR imaging helps to discover the largest malformation compartments remaining to be treated.

6.3. Treatment results; lymphangiomas
Those patients who had complete or marked regression in their lesions were treated with OK-432 as first line treatment. This finding is contrary to a previous report by Brewis et al. (2000), where no statistically significant difference was found between shrinkage in the two groups (previous surgery vs. no previous surgery). In the present study those patients who had previously undergone surgical resection or received some other treatment responded only with marked or moderate regression for OK-432 therapy in spite of a larger number of treatment sessions and greater volumes of OK-432. Our results imply that OK-432 injections should form the first treatment in complicated cases. In non-radical surgery there is a high recurrence rate. However, recurrence of disease after OK-432 therapy seems to be unusual, although long-term results are still lacking.
Surgical intervention may also be needed after endovascular treatment of lymphangiomas. The main indications are cosmetic correction and microcystic lymphangiomas not responding to sclerotherapy.

6.4. Complications

In venous malformations complications from ethanol sclerotherapy are most often due to extravasation causing necrosis of the adjacent soft tissues. Clinically important complications like blistering and ulceration may occur, likewise nerve damage. Cardiopulmonary collapse needing resuscitation has also been reported (Yakes 1994, Chapot et al. 2002). Sodium tetradecyl sulphate is found to cause less soft tissue damage when extravasation occurs, but the results are not as good as with ethanol (Siniluoto et al. 1997). Svendsen et al. (1994) reported 10% complication rate in their 31 patient study group (soft tissue necrosis). Four patients out of 59 (7%) developed skin necrosis or blistering according to a report by Goyal et al. (2002). About half of the treated venous malformations developed skin ulceration after ethanol sclerotherapy according to a report by Shireman et al. (1997). Lee et al. (2001) reported a complication percentage of 26.7% in their 80-patient study group. In the present study the complication rate was distinctly lower: the major complication rate was 5.2%; one patient developed a transient facial nerve paresis, one patient presented with transient slight paresis of nervus radialis and one patient had skin ulceration which healed with local wound care.

The discrepancy in these results may depend on the amount of ethanol used during individual treatment sessions. In the present study the amount of ethanol injected at one treatment session was only half to two thirds of the estimated volume of the lesion. In contrast to previous reports using ethanol as a sclerosant we did not generally use any external compression to improve the filling of the cavities. This could be one reason why the number of skin necroses in our study population was fairly low, as there was no overfilling of the malformation.

In lymphangiomas intralesional injection of various sclerosing agents such as alcohol, boiling water, and bleomycin have been used for treatment (Smith et al. 1996, Dubois and Garel 1999, Greinwald et al. 1999). These may spread outside the thin-walled lesions and cause damage to the surrounding structures making subsequent surgery difficult and involving extensive scarring. The results of this study confirm the previous reports that the complication rate for OK-432 sclerotherapy is low. When injected into the cystic spaces it produces sclerosis that does not spread outside the lesion (Greinwald et al. 1999). The only potentially serious side effect in the present study population was upper airway compression due to acute swelling of the lymphangioma.
6.5. Cost analysis

Only few cost identifications for interventional radiological units have been done, and before this study presumambly none that have been done using ABC analysis. ABC accounting was originally designed at 1980’s for use in industry and service producing units (Kaplan and Cooper 1998). It has also been found to suit well for analysing the service units of health care (Chan 1993). ABC analysis is based on the principle that activity creates costs; unlike in conventional accounting, where the products create the costs. When using ABC accounting, indirect costs especially are allocated to products more accurately than in conventional accounting. Besides identifying the cost factors, one can analyze them in the different activities. The ABC system was chosen to perform the cost calculations, because it makes it possible to trace the different activities giving a more precise allocation of the costs in the activities and final products (Chan 1993). Perhaps the most interesting finding was that the material costs are the most important cost factor in interventional radiology, especially in more complicated endovascular procedures. This was emphasized especially when the costs of sclerotherapies and microcatheter embolizations were compared. In spite of the high cost of angiography equipment its share of the costs is minor.

The current first line treatment for low-flow malformations is endovascular therapy, also at Tampere University Hospital. Therefore there was no comparable study population for cost comparison between surgery and endovascular therapy. Surgery would presumably be more expensive, due to the longer stay on the ward after the surgical procedure. After endovascular therapy the patients leave the hospital the same day or the day after. The costs of the operating theatre at the Interventional Radiology and Surgical Department would presumably be about the same, likewise the costs for anesthesia.
7. SUMMARY AND CONCLUSIONS

The present study confirms that endovascular treatment of low-flow malformations is safe and reliable. To achieve the best possible results, it demands fluent teamwork between radiologists and clinicians, as well as following up the patient with clinical visits. Gathering enough experience creates the best benefits for this small group of patients. Ethanol was found to be a reliable and safe sclerosant in treating venous malformations. The new sclerosant OK-432 was found to yield the best outcome so far in treating lymphatic malformations and there were far fewer recurrences compared to other treatment options.

In this study several prognostic factors were discovered which may help future decision-making concerning the appropriate planning of endovascular treatment and improve the general prognosis of treatment results for venous malformations. The importance of accurate pre-treatment imaging cannot be overemphasised and MR imaging was found to be the most useful technique. MRI characterizes the lesion, evaluates its extent, reveals possible high-flow components, and facilitates the planning of appropriate therapy for individual patients. Clinical control performed by physicians specialized in vascular malformations was found to be the most appropriate method of follow-up. In certain cases imaging control is needed, especially when clinical examination may be more complicated regarding possible small residual lesions such as in the face and neck.

Repeated therapy is usually required and the treatment may be protracted for a long time. In cases where the clinical condition does not improve despite ongoing treatment one should confirm the diagnosis of venous malformation with new imaging. Mixed lesions are quite common and high-flow components may maintain the symptoms. In these cases MR imaging is the preferable control imaging.

A conclusion from the results of the present study is that the questionnaire on quality of life evaluates patients’ state of health more accurately than pure subjective opinion. With the help of this questionnaire several notable correlations between quality of life and various pre-treatment and post-treatment parameters were discovered that were not found when comparing patient’s opinion to the same parameters. Quality of life analysis includes 20 multiple-choice questions, and is easy and fast to perform in conjunction with the clinical control after endovascular treatment. On the basis of this study it is advisable to use it in everyday practice, in order to achieve best optimal treatment results for individual patients with venous malformation.

ABC accounting proved to have satisfactory accuracy in the present study. ABC accounting deserves to be utilized in decision-making, especially when interventional radiology and surgical treatment are in the same square, and the costs play a part in decision-making for the treatment of choice.
8. ACKNOWLEDGEMENTS

The present study was carried out in the Department of Radiology in collaboration with the Department of Otolaryngology and Department of Vascular Surgery at Tampere University Hospital during the years 2000-2004. I wish to express my gratitude to all those who have helped me in my work with this thesis. I am particularly grateful to:

Professor Erkki M. Laasonen, who was the official supervisor of this study and gave valuable advice and support throughout the work.

Docent Leo Keski-Nisula, M.D., Ph.D., for suggesting me this topic to study and for giving me the clinical material. Moreover, I am thankful for the knowledge in vascular malformations he shared with me during this study.

Professor Hannu Manninen, M.D., Ph.D., for the guidance and constructive criticism throughout the study. He also reviewed the final manuscript.

Pekka Keto, M.D., Ph.D., for reviewing the final manuscript.

Jussi Laranne, M.D., Ph.D., and Jukka Saarinen, M.D., Ph.D., who carried out all the clinical controls.

Veikko Kähärä, M.D., Ph.D., who participated in film reading of the magnetic resonance examinations.

Docent Seppo Seppänen, M.D., Ph.D., who originally started the endovascular interventions in the Department of Interventional Radiology at Tampere University Hospital.

Ms. Virginia Mattila for revising the English language of the manuscript.

This study was financially supported by Medical Research Fund of Tampere University Hospital, Turku University Central Hospital, Radiological Society of Finland and The Finnish Medical Foundation.
9. REFERENCES


