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Vasospasm, its Role in the Pathogenesis of Diseases with Particular Reference to the Eye

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Abstract—Vasospasm can have many different causes and can occur in a variety of diseases, including infectious, autoimmune, and ophthalmic diseases, as well as in otherwise healthy subjects. We distinguish between the primary vasospastic syndrome and secondary vasospasm. The term "vasospastic syndrome" summarizes the symptoms of patients having such a diathesis as responding with spasm to stimuli like cold or emotional stress. Secondary vasospasm can occur in a number of autoimmune diseases, such as multiple sclerosis, lupus erythematosus, antiphospholipid syndrome, rheumatoid polyarthritis, giant cell arteritis, Behcet's disease, Buerger's disease and preeclampsia, and also in infectious diseases such as AIDS. Other potential causes for vasospasm are hemorrhages, homocysteinemia, head injury, acute intermittent porphyria, sickle cell disease, anorexia nervosa, Susac syndrome, mitochondriopathies, tumors, colitis ulcerosa, Crohn's disease, arteriosclerosis and drugs. Patients with primary vasospastic syndrome tend to suffer from cold hands, low blood pressure, and even migraine and silent myocardial ischemia. Valuable diagnostic tools for vasospastic diathesis are nailfold capillary microscopy and angiography, but probably the best indicator is an increased plasma level of endothelin-1. The eye is frequently involved in the vasospastic syndrome, and ocular manifestations of vasospasm include alteration of conjunctival

vessels, corneal edema, retinal arterial and venous occlusions, choroidal ischemia, amaurosis fugax, AION, and glaucoma. Since the clinical impact of vascular dysregulation has only really been appreciated in the last few years, there has been little research in the according therapeutic field. The role of calcium channel blockers, magnesium, endothelin and glutamate antagonists, and gene therapy are discussed. © 2001 Elsevier Science Ltd. All rights reserved

1. INTRODUCTION

Vasospasm plays a major role in the pathogenesis of a number of diseases, both in the eye and elsewhere in the body. Whereas the role of vasospasm in the pathogenesis of glaucomatous damage is well described (Flammer *et al*., 1990; Flammer, 1992), this review attempts to bring vasospasm into a broader medical context. Different causes, pathophysiology, clinical aspects as well as potential therapeutic consequences are discussed.

1.1. What is vasospasm?

Vasospasm is defined as inappropriate constriction or insufficient dilatation in the microcirculation (Flammer, 1996). Because such vasoconstrictions are often combined with simultaneous arterial or venous dilatations in neighboring vessels (Flammer and Prünte, 1991) or in other vascular beds, we introduced the term ''vascular dysregulation'' (Flammer, 1998a,b; Flammer *et al*., 1999). Although such dysregulation is involved in the pathogenesis of many different diseases, clinicians have rather neglected its importance. However, the recognition of vasospasm is essential both for the understanding and the treatment of a number of diseases.

Vascular dysregulations have many different causes and occur in many different organs. This review summarizes some pathophysiological and clinical impacts of vascular dysregulations in the pathogenesis of different diseases, with special emphasis on eye diseases.

Vasospastic disorders are often falsely equated with Raynaud's disease or even migraine. Raynaud's phenomenon describes attacks of reversible finger ischemia which may occur with or without an underlying disease, and with or without digital vessel obstruction (Mahler *et al*., 1989). Some of these patients indeed have a generalized vasospastic syndrome. On the other hand, patients with a vasospastic syndrome, although often presenting with cold hands, rarely have the classical symptoms of attacks with pale fingers (i.e. do not have Raynaud's disease).

The inter-relationship between the vasospastic syndrome and migraine is not yet well established. Although patients with migraine suffer more frequently from a vasospastic syndrome than normal individuals (Hegyalijai *et al*., 1997), not all vasospastic patients have migraine, and not all migraine patients have a vasospastic syndrome. Vasospasm occurring during migraine attacks will be discussed later.

1.2. Where do vasospasm occur?

Vascular dysregulations occur ubiquitously. However, some organs might be more prone towards spasm, whereas in other organs spasms may only occur rarely, or if they occur they may be of little clinical relevance. As yet unrecognized clinically relevant vasospasm may also exist. Spasms are very well described in the fingers, the heart, the brain and the eye (Gasser *et al*., 1986). Although dysregulation occurs in vessels of different sizes, it is mainly located within the microcirculation. Whereas constriction in resistance vessels might be involved in the pathogenesis of systemic hypertension, the dysregulation in the vasospastic syndrome is generally localized to the small arterioles and venules and the capillaries.

1.3. What is the cause of a vascular dysregulation?

Many factors and conditions lead to a vascular dysregulation. There is a large group of vasospastic patients without any concomitant diseases. Most have a genetic predisposition to respond with vasospasm (see Section 4.1), and we therefore introduced the term ''vasospastic diathesis'' (Flammer *et al*., 1992). At present little is known about the genes involved. The term vasospastic syndrome (Flammer, 1996) summarizes the

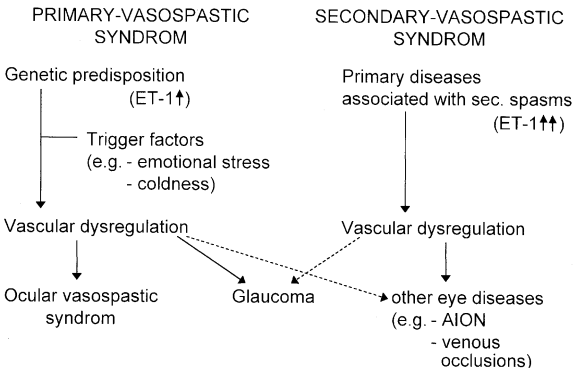

Fig. 1. Relationship between primary and secondary vasospasm with ocular diseases.

symptoms of patients having such a diathesis as responding with spasm to stimuli like cold or emotional stress (see Section 4.4). If the syndrome occurs without an underlying disease we call it "primary vasospastic syndrome" (Fig. 1). This syndrome is of special interest for the ophthalmologist as the spasm most commonly involves the eye (Gasser *et al.*, 1986). Beside this primary diathesis, many diseases can lead to vasospasm, as can be demonstrated even in animal models. We describe these situations as "secondary vasospasm" (Fig. 1).

There are some general factors that influence the prevalence of vasospasm. It is more frequently observed in females than in males (Flammer and Prünte, 1991), rarely occurs before puberty, and often decreases after menopause. There also appears to be an ethnic influence. The vasomotor response differs between black and white subjects. The primary vasospastic syndrome is more prevalent in Japanese than in Caucasian patients (Beltrame *et al.*, 1999), which might explain why some related diseases, such as normal tension glaucoma, are more prevalent in Japan than in other countries.

There is, furthermore, a complex interplay between spasm and ischemia. Spasm can lead to ischemia while ischemia itself can provoke spasm, thereby creating a vicious circle.

1.4. How to diagnose spasm?

Spasm in the fingers can easily be recognized on the basis of a patient history of cold hands (Mahler *et al.*, 1989). However, spasm in some other organs can be difficult to diagnose. The most specific and sensitive diagnostic tool is angiography. Spasm in many organs such as the brain has been demonstrated with angiography, but this diagnostic intervention is often too invasive and therefore reserved for special indications. Nevertheless, there are many signs and symptoms indicative of vasospasm, or at least of a predisposition to respond with vasospasm, and which are especially helpful for detection of a primary vasospastic syndrome. Patients with presumed primary vasospastic syndrome tend to have cold hands (and sometimes cold feet) more frequently than the average population (Flammer and Prünte, 1991). They also tend to have low blood pressure, especially during the night. The conjunctival vessels show quite characteristic changes (Orgül and Flammer, 1995) (Fig. 2). Note that such alterations can change quickly from one day to the other, and often disappear upon local application of eye drops (for example mydriatics).

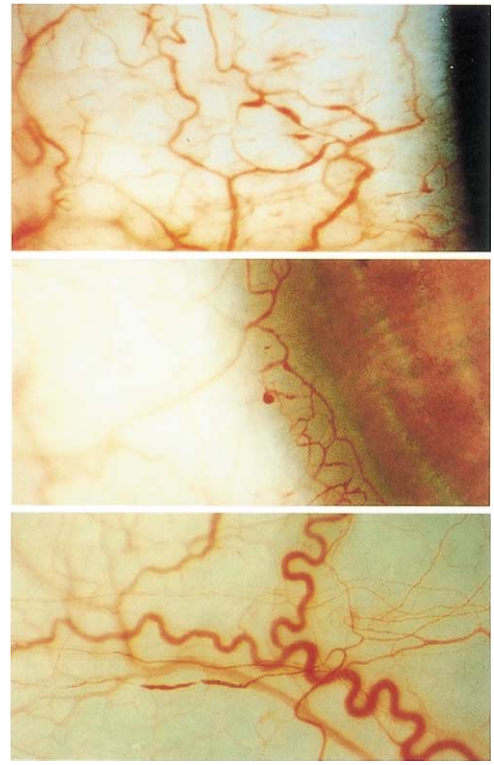

Fig. 2. Alterations of conjunctival vessels in patients with vasospasm.

Of great diagnostic value is nailfold capillary microscopy (Fig. 3). The capillaries of the nailfolds can be directly visualized under the microscope (Saner *et al.*, 1987). A reduced baseline blood flow velocity, and especially a prolonged flow stop after cold provocation, can be observed (Gasser, 1990). Although video nailfold capillaromicroscopy combined with a cold provocation is a very useful noninvasive diagnostic tool, it should be emphasized that a normal outcome does not exclude either vasospasm in other parts of the body, or vasospasm provoked by stimuli other than cold. Probably the best diagnostic indicator is an increased level of endothelin-1 in the circulating blood, but effective exploitation of this diagnostic tool requires a good laboratory and dependable normal values (Miyauchi and Masaki, 1999).

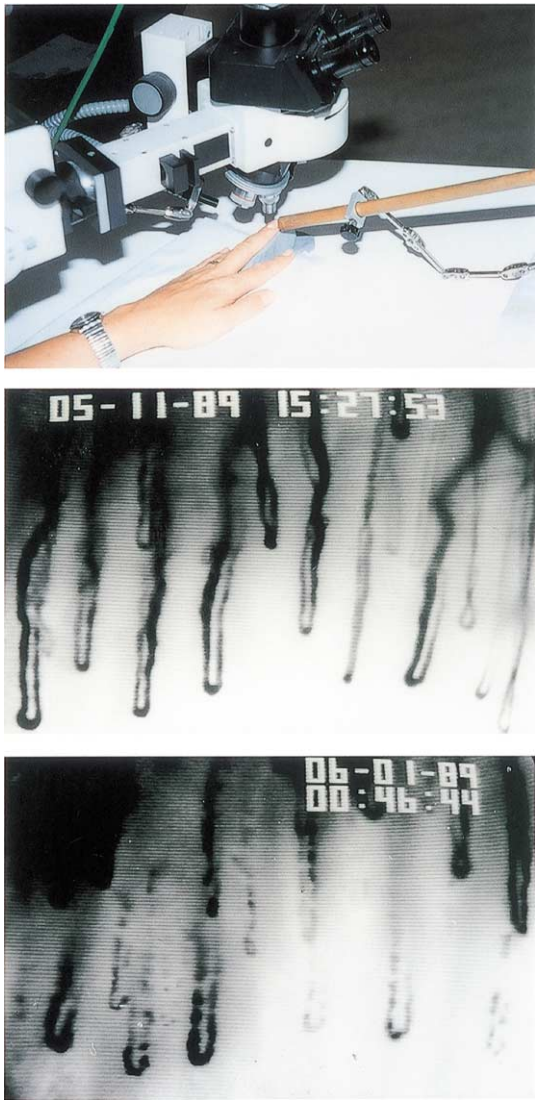

Fig. 3. Upper panel: Setting of the nailfold capillary microscopy. Middle panel: Normal nailfold capillaries. Lower panel: Spastic nailfold capillaries.

2. PRIMARY VASOSPASTIC SYNDROME

There are people who, throughout their lives, respond to stimuli such as cold or emotional stress with more frequent and more intense vasospasm than the average population. In clinical terms they are often designated ''vasospastic patients'', and if the vasospasm is not a consequence of any other disease, we refer to a ''primary vasospastic syndrome''.

2.1. The primary vasospastic syndrome in general

The principle symptoms of patients with primary vasospasm are cold hands, sometimes cold feet, and a tendency towards low blood pressure. Some of the patients suffer from migraine, but the relationship between the vasospastic syndrome and migraine is rather weak. This will be discussed later. Vasospastic patients generally have a low body mass index, but spasm can occur even in obese patients. The syndrome appears more frequently in intellectual people and females than in craftspeople and males. It normally starts in puberty, and in females it often decreases markedly after menopause. Some patients suffer from low blood pressure whilst young but then exhibit a higher blood pressure as they get older. Because blood pressure fluctuates markedly in these patients, only a 24 h blood pressure monitoring can reveal the so-called, mostly nocturnal, ''dips'' or ''overdips''. Some of the patients also suffer from orthostatic hypotension. Since the majority of patients report on similar symptoms in their mother and sometimes also their father, there appears to be some genetic predisposition.

Vasospastic patients are generally less thirsty than the average population, and disclose that they drink because they know they have to drink and not because they are thirsty. This phenomenon can

be explained by an increased endothelin-1 level (Fitzsimons, 1998). Some of the patients are also hypersensitive to drugs such as beta blockers or calcium channel blockers. In such patients the desired pharmacological effect can be achieved by a very low dosage of a given drug. We have some indications that this is due to lack of an ABC transport protein (unpublished data).

It should be reiterated that subjects presenting with the vasospastic syndrome are otherwise healthy, and that the spasms are mostly relatively harmless and do not need treatment. The syndrome does, however, predispose toward some diseases as discussed later.

2.2. The involvement of the eye

In the early eighties we observed that patients with vasospastic disorders often had visual field defects (Gasser and Flammer,1987, 1991). Such patients are not aware of their visual handicap since their visual acuity is normal and the visual field defects generally are diffuse. We further observed that such visual field defects could be provoked by cold and improved by calcium channel blockers in patients with vasospastic diathesis but not in normals (Guthauser *et al.*, 1988). We thus postulated an involvement of the visual system in the vasospastic syndrome. If the visual field defects were more localized, they were not homogenous, and we concluded that the lesions must be prechiasmal. Retinal vasospasm could be more or less excluded since no changes in the retina could be observed, at least in the majority of the patients. Therefore, we postulated vasospasm in the ciliary or choroidal circulation and probably also in the optic nerve head, and introduced the term "presumed ocular vasospastic syndrome" (Flammer *et al.*, 1992).

The optic nerve heads of these patients are mostly normal, especially when they are young. Some of the patients have slightly pale optic nerve heads, which often leads to a differential diagnosis of multiple sclerosis. Both diseases occur more often in young females, can prolong the latency of visually evoked potentials, and as can be detected with MRI there may be lesions in the brain. A clear relapse with neurological symptoms or the presence of oligoclonal antibodies in the CSF then clearly confirms diagnosis of multiple sclerosis. But we stress that patients with multiple sclerosis often do have a secondary vasospastic syndrome. This will be discussed.

A minority of the patients with ocular vasospastic syndrome eventually develop optic nerve head excavation (Fig. 4). This led us to hypothesize that vasospasm might be an important risk factor for glaucomatous damage (see Section 9).

Although the eye is often involved in secondary spasm, primary vasospasm plays an even more important role for the eye, and only the primary

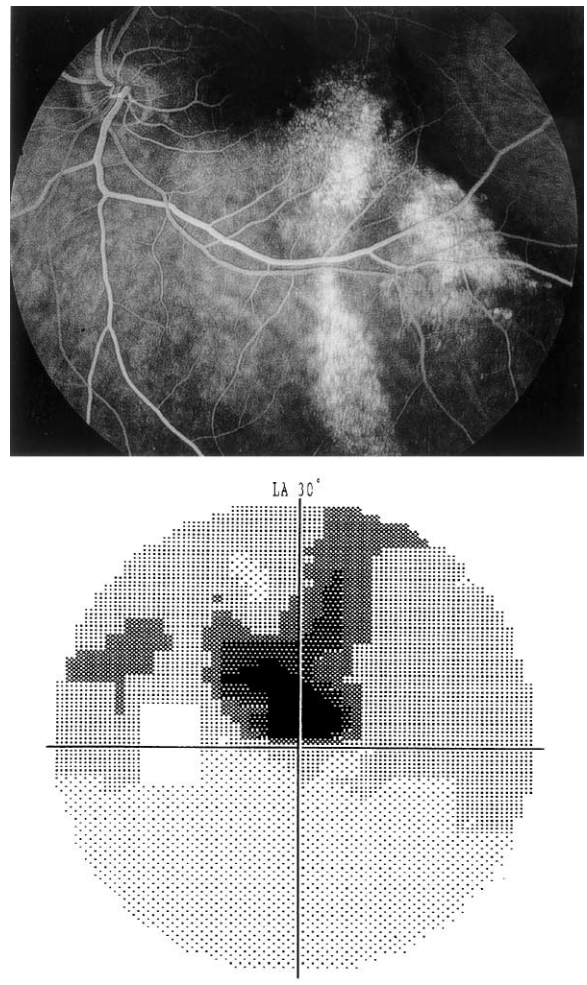

Fig. 4. Choroidal infarction in a vasospastic patient. Upper panel: Fluorescence angiography. Lower panel: Octopus perimetry.

vasospastic syndrome is a clear risk factor for glaucomatous damage (Gasser and Flammer, 1991).

3. SECONDARY VASOSPASM

Vasospasm occur concomitantly with many different diseases. Although we do not know exactly why these diseases also provoke spasm, it is evident that an increased concentration of endothelin-1 is common to all of these diseases (see below and Section 4). Vasospasm, combined with an increased plasma endothelin-1 concentration has been observed especially in autoimmune diseases.

3.1. Vasospasm in patients with autoimmune diseases

Autoimmune diseases can lead to ischemia in many ways including thrombosis. Clinical observations, however, prompted us to assume that autoimmune diseases may also lead to functional vascular dysregulation. In the following, some of these autoimmune diseases are briefly discussed.

3.1.1. *Vasospasm and multiple sclerosis*

The relationship between vasospasm and multiple sclerosis (MS) is very interesting. On one hand a severe primary vasospastic syndrome can mimic the symptoms of multiple sclerosis. We have observed a number of patients with so-called "atypical MS" who were later found to be suffering from a severe vasospastic syndrome and not from MS. On the other hand, we have observed that patients with MS suffer more frequently from vasospastic symptoms than the average population. They often have cold hands or decreased thirst. Moreover, patients with MS have significantly increased levels of endothelin-1 in the blood (unpublished data) and in the cerebrospinal fluid (Speciale *et al.*, 2000). We observed a further rise of plasma endothelin-1 during retrobulbar neuritis (unpublished data). We postulate therefore that MS can provoke secondary vascular dysregulations. Most probably not only endothelin-1 but many other as yet not detected vasoactive factors (e.g. prostaglandin E_2), are involved. These may contribute to alterations such as retinal "vasculitis" or pale optic nerve head in the eye. The exaggerated increase of endothelin-1 during an acute retrobulbar neuritis may account, in part, for the reversible visual loss in such patients.

3.1.2. *Giant cell arteritis*

In patients with giant cell arteritis (GCA), a marked decrease of ocular perfusion, especially of the choroid, can frequently be observed (Fig. 6). There are several hints that such a reduction in blood flow may not only be a direct consequence of an occlusive vasculitis but might also indirectly result from vascular dysregulation. In contrast to the non-arteritic AION, nitroglycerin and systemic calcium channel blockers often improve visual defects in GCA. The increased prevalence of amaurosis fugax, non-thrombembolic retinal artery occlusions and cotton wool exudates in GCA supports the hypothesis of secondary vasospasm (Lübeck *et al.*, 1998). We indeed find increased endothelin-1 plasma levels in patients with GCA (unpublished data). An increased endothelin-1 level is known to reduce choroidal blood flow. This may also explain glaucoma-like alterations of the optic nerve head seen in GCA (Orgül *et al.*, 1994). In animal experiments, locally applied endothelin-1 induced optic nerve head ischemia leads to axonal loss and demyelination affecting the prelaminar portion of the optic nerve (Oku *et al.*, 1999) and to an increase in intraocular glutamate concentration (Kim *et al.*, 2000).

3.1.3. *Lupus erythematosus*

Lupus erythematosus (LE) describes a group of connective tissue disorders which primarily affect women between twenty to forty years old, and encompasses a spectrum of clinical conditions in which the skin disease may occur with or without systemic involvement. Systemic LE (SLE) predisposes not only to Raynaud's syndrome but even to myocardial infarction in very young people (Fearon and Cooke, 1996). Plasma endothelin-1 levels are increased, and sera from patients with SLE can induce endothelin-1 release from cultured endothelial cells (Yoshio *et al.*, 1995). A reversal of the vasospastic components in lupus vasculopathy

can be achieved by infusion of prostaglandin E1 (Hauptman *et al.*, 1991).

3.1.4. *The antiphospholipid syndrome (APS)*

Antiphospholipid antibodies (APA) are a heterogeneous group of immunoglobulins originally thought to recognize anionic phospholipids, and were first documented in SLE patients with an increased risk of thrombosis. The antibodies are directed against different antigens, in particular cardiolipin, β2 glycoprotein, and phosphatidylserine. Diverse clinical features besides thrombotic events include pulmonary hypertension, thrombocytopenia or migraine (Vayssairat *et al.*, 1997). Recurrent cerebral ischemic attacks may lead to a multi-infarct dementia. There are indications that some of the occlusions might be due to vasospasm (Nomura *et al.*, 1998). Abnormalities in the nailfold capillary microscopy are described (Sulli *et al.*, 2000), and endothelin-1 is increased in these patients (Atsumi *et al.*, 1998). An association of APA with retinal vascular occlusions are described both in patients with and without SLE (Montehermoso *et al.*, 1999; Leo-Kottler *et al.*, 1998). Interestingly, APA are also found more frequently in normal-tension glaucoma patients than in normals (Tsakiris *et al.*, 1992).

3.1.5. *Rheumatoid arthritis*

Rheumatoid arthritis is a chronic multi-system disease of presumed autoimmune etiology. It is estimated that about one percent of the population is affected by this disease. Besides some general symptoms such as fatigue and muscle pain, the main indication is a synovitis leading to marked changes of the joints. A number of other organs can be involved including the eye, where episcleritis and scleritis as well as kerato-conjunctivitis with a dry eye syndrome can occur. Tissue hypoxia due to vasospasm including a Raynaud phenomenon is often associated with the disease (Fischer *et al.*, 1984). Human synoviocytes produce endothelin-1 (Yoshida *et al.*, 1998). Plasma endothelin-1 levels are increased, and endothelin-1 blockers reduce both the inflammatory process and the pain (Miyasaka *et al.*, 1992). Endothelin-1 receptors have been localized in synovial tissue (Wharton *et al.*, 1992).

3.1.6. *Behcet's disease*

Behcet's disease is a chronic relapsing-remitting vasculitis in young adults. Its clinical features include synovitis and thrombophlebitis. Different organs such as lung, gastrointestinal tract, and central nervous system can be involved. Uveitis is a common ocular manifestation of Behcet's disease. Sometimes this is associated with vascular occlusions. Further manifestations are optic neuropathy, retinal and optic disc atrophy, neovascular glaucoma, hemorrhage, retinal tears and retinal detachment. In fluorescein angiography, a delayed choroidal filling and a leakage from the optic disc is often observed (Krist *et al.*, 2000). With the help of Color Doppler Imaging changes in flow velocities of the posterior segment compared with control subjects have been described (Celebi *et al.*, 2000). Plasma endothelin-1 levels are elevated (Uslu *et al.*, 1997). Interestingly, in these patients acetazolamide infusion increases regional cerebral blood flow in areas with decreased perfusion, but not in areas of normal perfusion (Pupi *et al.*, 2000).

3.1.7. *Buerger's disease*

Buerger's disease, also called thrombangiitis obliterans, occurs mainly in young males and cigarette smokers. Vascular occlusions occur mostly in the lower extremities, but can occur even in the eye (Bernardczykowa and Zawilski, 1991). The disease can be associated with increased anticardiolipin antibodies and hyperhomocysteinemia. Examination by high-resolution arterial subtraction angiography revealed functional vasospastic disorders dominating the early stages of the disease (Bauer *et al.*, 1990). Furthermore, thrombangiitis obliterans can cause a reversible Raynaud's phenomenon (Noel *et al.*, 2000).

3.1.8. *Preeclampsia*

Preeclampsia is a complication of pregnancy characterized by hypertension, edema and proteinuria. It occurs more frequently in women with

connective tissue diseases and an immunological component has thus long been suspected (Taylor, 1997). Vasospasm, especially of the cerebral vessels, is a major component of preeclampsia (Hansen *et al*., 1996) and may also be the cause of transient cortical blindness (Niehaus *et al*., 1999). Retinal vasospasm has also been observed (Belfort and Saade, 1993). Severe vasospasm can result in choroidal ischemia leading to serous retinal detachment (Lee *et al*., 1999). Plasma endothelin-1 level is increased in these patients (Bussen *et al*., 1999). An increased expression of NO synthase isoforms further supports the presumption of a vascular dysregulation (Napolitano *et al*., 2000).

3.2. Infectious diseases

Relatively little is known about the relationship between infectious diseases and vascular dysregulation. Severe hypoxia and infarctions are associated with infections. However, it is difficult to distinguish between hypoperfusion due to mechanical alterations of blood vessels, and hypoperfusion due to functional dysregulation.

3.2.1. *Bacterial infection*

In a number of bacterial infections endothelin-1 is increased. Endotoxin stimulates endothelin-1 production in peripheral monocytes (Ebihara *et al*., 1998). Endothelin-1 is increased in patients with bacterial meningitis (Koedel *et al*., 1997), and might be one of the causes for concomitant cerebral infarctions. It is assumed that the intestinal hypoperfusion during bacteremia might be due to increased levels of endothelin-1 (Wilson *et al*., 1993). In sepsis, endothelial cells release endothelins, NO and products of cyclo-oxygenase metabolism, thus leading to microcirculatory dysfunction (Wort and Evans, 1999).

3.2.2. *Viral infections*

Some viral infections may lead to vasospasm. Adenovirus infections, for example, can increase endothelin-1 levels by increasing expression of endothelin-converting enzyme (Telemaque *et al*., 1998). Endothelin-1 is also increased in patients with viral liver cirrhosis. It is assumed that increased levels of endothelin-1 plays an important role in the aggravation of portal hypertension in liver cirrhosis (Abdel-Rahman *et al*., 1995).

More is known about vasospasm and endothelin-1 in patients with a HIV-infection. AIDS-patients with retinal microangiopathy have a marked increase in endothelin-1 (Rolinski *et al*., 1994). This ocular microangiopathic syndrome is often associated with cognitive deficits. AIDS patients may even have digital necrosis due to the vasculopathy (Roh and Gertner, 1997). Bilateral central retinal vein occlusion has been described (Friedman and Margo, 1995). It is now known that monocytic endothelin-1 production in these patients is stimulated by the HIV-1 glycoprotein 120 (Ehrenreich *et al*., 1993). We are presently investigating the influence of virostatic treatment on both endothelin-1 levels and the microcirculation in HIV-infected patients.

3.3. Other potential causes

Based on clinical experience a number of other diseases and other factors might be able to elicit spasm. Some of these causes are already well documented in the literature, others are still hypothetical.

3.3.1. *Hemorrhages*

Both clinical and experimental studies on brain hemorrhages have demonstrated that extravascular blood components can induce vasospasm (Maeda *et al*., 1997). The vasoconstrictions normally occur a few days after the bleeding and can persist for days or weeks. The constrictions may be due to the binding of NO by hemoglobin. Endothelin-1 seems to play an even more important role (Secades *et al*., 2000). The reduction of endothelin-1 production, as well as administration of endothelin-1 blockers have been shown to be useful in the treatment of such spasm (Ohkuma *et al*., 1999). On the other hand, it also has been reported that severe spasm during migraine attack may lead to brain hemorrhages (Nakamura *et al*., 1997).

We have postulated that hemorrhages in the optic nerve head, since they typically occur in glaucoma and especially in normal tension

glaucoma, may not be the consequence but rather the cause of a microinfarction (Orgül and Flammer, 1994). This would explain why the visual field defect normally appears a few days after the acute bleeding (Airaksinen *et al.*, 1981).

3.3.2. *Homocysteinemia*

It has been known for some time that homocystinuria, a rare inborn error of metabolism, can be due to genetic mutations that severely disrupt homocysteine metabolism. A more recent finding is that milder, but more common, genetic mutations in the same enzymes might also contribute to an elevation in plasma homocysteine. Homocysteinemia is an independent risk factor for cardiovascular disease. Vasospasm has been reported as a manifestation of homocysteinemia (Katzenschlager *et al.*, 2000). A close relationship between homocysteine, neopterin and endothelin-1 has been described, suggesting that homocysteine exerts its deleterious effect on vascular function through interference with endothelial and leukocyte function (Gottsater *et al.*, 2000). Furthermore, homocysteinemia causes abnormal magnesium metabolism in cerebral vascular smooth muscle cells, thus priming these cells for atherogenesis, cerebral vasospasm and stroke (Li *et al.*, 1999).

3.3.3. *Head injury*

Several blood flow studies in cases with severe head injury have revealed brain ischemia in a substantial number of patients (Schroder *et al.*, 1998). Data available support the hypothesis that vasospasms are the cause of early ischemia in such patients (Martin *et al.*, 1997).

3.3.4. *Acute intermittent porphyria*

Acute intermittent porphyria (AIP) is an autosomal-dominant disease caused by a deficiency of porphobilinogen deaminase. Typical symptoms are abdominal pain, hypertension and neurological syndromes including convulsions. Permanent blindness (Lai *et al.*, 1977) as well as transient cortical blindness (Kupferschmidt *et al.*, 1995) and a variety of further cerebral lesions due to severe vasospasm have been described.

3.3.5. *Sickle cell disease*

Sickle cell disease is caused by a mutation in the beta-chain of the hemoglobin molecule. The resulting sickle hemoglobin has the singular property of polymerizing when deoxygenated. Exactly how tissue perfusion is interrupted by sickle cells is complex and poorly understood. The contribution of microvascular inflammation and vascular dysregulation in the development of an acute sickle cell crisis have been intensively studied. It is presumed that vasospasm plays an important role in the pathophysiology of sickle cell disease. With respect to the eye, nifedipine treatment of a sickle cell crisis leads to reversal in ischemic retinal and conjunctival changes, as well as to a significant improvement in color vision performance (Rodgers *et al.*, 1988). Endothelin-1 levels are increased, with a further increase during the acute vaso-occlusive crisis. It is presumed that endothelin-1 contributes both to the prolonged spasm and to the inflammation in sickle cell disease. Therefore, patients may benefit from endothelin antagonists (Graido-Gonzalez *et al.*, 1998).

3.3.6. *Anorexia nervosa*

Anorexia nervosa is primarily a psychiatric disorder occurring predominantly in females with a usual onset in adolescence. It is characterized by weight loss due to a refusal to maintain a normal minimal body weight and an intensive fear of becoming obese. Etiological research indicates not only a complex interaction among psychological and socio-cultural factors, but also suggests a substantial genetic influence in this disorder. Obsessive, perfectionist, and anxious personality styles may be premorbid traits that contribute to this pathogenesis (Kaye *et al.*, 2000). Interestingly, these patients normally have cold hands, and occasionally also suffer from perniosis, acrocyanosis and peripheral vasculopathy (Bhanji and Mattingly, 1991). The disorder can also lead to abdominal angina (Bircher *et al.*, 1966) and to central retinal vein occlusion (Shibuya

and Hayasaka, 1995). We have observed cilioretinal artery occlusion combined with retinal vein occlusion in patients with anorexia nervosa.

3.3.7. *Mitochondriopathies*

Mitochondriopathies are a large group of diseases in which the mitochondrial function is defect, mostly as a result of a mutation of the mitochondrial DNA. We have described this mitochondrial function elsewhere (Flammer, 1999). In ophthalmology the most important mitochondriopathy is the Leber's hereditary optic neuropathy (LON). The vast majority of our patients with LON suffer from vasospasm (Flammer, 1999). However, this fact is most probably not due to point mutations in the mitochondrial DNA. We rather assume that the vasospastic disorder (like some other factors) may trigger the disease in patients that carry the mutation.

3.3.8. *Tumors*

Malignant tumors can cause many different symptoms that are not yet well explained. They are often collectively described under the term "paraneoplastic syndrome". One of the symptoms occurring in such patients is a Raynaud's phenomenon (Taillan *et al*., 1993), indicating that vascular dysregulation may occur in cancer patients. A marked increase of endothelin-1 has been observed especially in patients with metastatic adenocarcinoma of the prostate (Pirtskhalaishvili and Nelson, 2000). Furthermore, endothelin-1 has been identified as a potential factor in the osteoblastic response to metastatic prostate cancer (Nelson *et al*., 1999). We have observed ischemic optic neuropathy in such patients. A causal relationship is possible.

3.3.9. *Colitis ulcerosa and Crohn's disease*

The majority of patients with Crohn's disease have acral vasospasm as demonstrated by capillaromicroscopy (Gasser *et al*., 1991). This can cause retinal vascular diseases (Keyser and Hass, 1994) or even occlusion of the ophthalmic artery (Bonvin *et al*., 1994). Patients with Crohn's disease or Colitis ulcerosa have increased levels of endothelin-1 (Murch *et al*., 1992). In animal models, endothelin antagonists showed a positive therapeutic effect on colitis (Padol *et al*., 2000). It can therefore be presumed that endothelin-1 also plays a role in the pathophysiology of the chronic inflammatory process.

3.4. Drugs

Vasoconstriction is the major pharmacological effect of some drugs, for example sympathomimetics. Adrenaline can induce a variant angina (Rubio-Caballero *et al*., 1999). Anterior ischemic optic neuropathy was observed following the use of nasal decongestant (Fivgas and Newman, 1999). For other drugs vasoconstriction is not the main pharmacological effect but rather a pronounced side effect. For example, vasospasm-induced myocardial infarction was observed with sumatriptan (Mueller *et al*., 1996). A Raynaud's phenomenon can be provoked by beta blockers such as timolol (even when applied locally to the eye) (Meuche *et al*., 1990). Bilateral transient obscuration during α-II interferon therapy was observed in patients with known Raynaud's syndrome (Detry-Morel *et al*., 1995). Bilateral ischemic optic neuropathy was observed secondarily to acute ergotism (Sommer *et al*., 1998). Depending on the tissue, local anaesthetics can induce vasodilatation or vasoconstriction. Ocular perfusion is drastically reduced after retrobulbar anaesthesia. This is not primarily due to mechanical compression of the tissue, but rather to local interference with NO-production (Meyer *et al*., 1993). Visual loss has been observed even after intranasal anaesthetic injection (Savino *et al*., 1990).

The influence of sex hormones is controversially discussed in the literature. Natural estrogens seems to be protective against arteriosclerotic coronary diseases (Lüscher *et al*., 1996). Whereas estrogen may induce spasm in patients with spastic diathesis (Kaiser and Meienberg, 1993), progesterone seems to have an anti-spastic effect (Kanda and Endo, 1997). We have observed patients with primary vasospastic syndrome in which the spasm increased markedly after initiation of estrogen therapy. These spasm decreased after the cessation of the estrogen treatment. Migraine can deteriorate under estrogen replacement therapy during

menopause (Kaiser and Meienberg, 1993). Therefore, for patients with a vasospastic syndrome we recommend measurement of some vascular parameters of the ocular perfusion and a capillaromicroscopy before, and about three months after, the start of estrogen treatment. Continuation of estrogen therapy is encouraged if there is no deterioration or even improvement, while cessation of therapy, if possible, is recommended in the event of any deterioration.

3.5. Arteriosclerosis

It is often assumed that, for mechanical reasons, vasospasm do not occur in patients with arteriosclerosis. This is not correct. Arteriosclerotic vessels can constrict. However, the vascular dysregulation occurs mostly in the smaller vessels which are less affected by the arteriosclerotic process. Arteriosclerotic patients indeed have less vasospasm, but this is due to the fact that they are generally older. Whereas patients with a vasospastic syndrome tend to have an increased responsiveness to endothelin-1, especially when blood pressure is low (Gass *et al.*, 1997), patients with the syndrome X have reduced responsiveness (Newby *et al.*, 1998). Arteriosclerotic patients have another type of endothelial dysfunction (Vanhoutte, 1997) whereby there is a shift from a normally predominant release of endothelium-derived relaxing factors to a predominant release of endothelium-derived constricting factors. This may play a crucial role in local vasoconstrictions that, with or without thrombosis, lead to infarction. These vasoconstrictions are more localized, less recurrent and triggered by other factors than the spasm in the so-called primary vasospastic syndrome (Hellstrom, 1979). On the other hand, since recurrent vasospasm can lead to tissue damage and ensuing arteriopathy, it may participate in pathogenesis of arteriosclerosis (Gutstein, 1999). It should be noted that factors regulating the vascular tone are also involved in the long-term pathogenesis of arteriosclerosis. We have demonstrated that angiotensin II, when applied in combination with insulin, has a major influence on vascular structure (Dubey *et al.*, 1998). This explains why patients with type II diabetes, having systemic hypertension, have a higher risk for arteriosclerosis and diabetic retinopathy. On the other hand oxidized LDL (Ox-LDL), which plays a major role in the pathogenesis of arteriosclerosis, also possesses vasoconstrictive properties. We have shown that Ox-LDL-induced vasoconstriction is mediated by endothelin-1 since it can be abolished by endothelin-1 receptor antagonism (Zhu *et al.*, 1999). The post ischemic vasoconstriction is mediated by an increase of endothelin-1 and a reduction of NO production (Gidday and Zhu, 1998).

4. PATHOPHYSIOLOGY AND PATHOGENESIS

The pathophysiology of the spasm is not yet well understood. Diverse systems and factors are involved in the regulation of vascular tone. Thus, theoretically many different alterations such as a reduced NO production, increased sympathetic activation (inter alia) could lead to vasospasm. Moreover, it is unlikely that all spasm can be explained by a single factor. Rather, vasospasm may develop through very different pathomechanisms. The fact that vasospasm are a more or less localized phenomenon repeatedly affecting the same vascular bed indicates that a local dysfunction of the blood vessels might be involved. In the past, research interest was focused on a local hyper-responsiveness of the adrenergic nervous system. However, since phenylephrine and norepinephrine per se fail to precipitate spasm, the adrenergic nervous system is unlikely to play a primary role. Furthermore, spasm often occur during periods when the sympathetic nervous system is not activated.

4.1. The role of genetics

Clinical experience clearly indicates that the primary vasospastic syndrome at least has a genetic component. Vasospastic angina occurs more frequently in siblings (Tachibana *et al.*, 1995; Fournier *et al.*, 1986). There is a polymorphism of the angiotensin converting enzyme, and some types might underlie a greater risk for myocardial infarction (Oike *et al.*, 1995). There is evidence that HLA-DR2 increases susceptibility to coronary vasospasm (Horimoto *et al.*, 1998)

Additionally, a mis-sense Glu298 Asp variant in the endothelial nitric oxide synthase gene is associated with coronary vasospasm (Yoshimura *et al.*, 1998). An x-recessive angiopathic opticopathy has been described (Bastiaensen and Vandoninck, 1982). Nevertheless, in the majority of patients with vasospasm, the genes involved have not been identified.

4.2. The role of endothelin-1

Endothelin-1 is increased in patients with primary vasospasm or secondary vasospasm. Endothelin-1 is a 21-amino acid peptide produced mainly by vascular endothelial cells. Although the bulk of the peptide is secreted abluminally, endothelin-1 is also secreted intraluminally and thereby influences the circulating blood concentrations of the peptide. The lung plays a major metabolic role in removing endothelin-1 from the circulating blood. This would imply that in patients with vasospasm, either less endothelin-1 is extracted during passage through the pulmonary circulation or, and more likely, greater amounts of endothelin-1 are produced.

Endothelin-1 may induce a vascular hyperresponsiveness to various stimuli rather than being the direct cause of vasospasm. If so, increased endothelin-1 levels might be an essential, but insufficient, factor in triggering vasospasm. Increased concentrations of endothelin-1 potentiate constrictions to serotonin and norepinephrine in human coronary vessels. Endothelin-1 increases the calcium sensitivity of human arteries, and thereby interferes with fundamental intracellular mechanisms involved in the contractile process. However, it is also possible that high local concentrations of endothelin-1 are released abluminally towards the underlying vascular smooth muscle of a specific vascular segment prone to spasm (Zimmermann, 1997).

It is more difficult to assess the role of endothelin-1 in secondary vasospasm. It is known that interleukin-1, a peptide involved in inflammatory processes, is able to increase endothelin-1 production. An increase in metalloprotease activity may also increase the cleavage of prepro-endothelin to endothelin-1. Since endothelium-derived nitric oxide also participates in the regulation of endothelin-1 production via cGMP dependent mechanism, a reduced local function of endothelium-derived relaxing factors in the diseased vascular segment could contribute to an enhanced endothelin-1 production.

In consideration of the present knowledge we can conclude that an increased level of endothelin-1 is an apparent prerequisite for vasospasm. Endothelin-1 is apparently increased in all diseases related to vasospasm, even in patients with morbus Addison (Letizia *et al.*, 1996) or in patients with hypoparathyroidism (Letizia *et al.*, 1995). Additional factors, such as prostaglandins might also be involved, but of greatest importance are those factors that trigger spasm in predisposed patients.

4.3. The role of magnesium

An association between magnesium (Mg) deficiency and vasospasm is suggested by a substantial number of studies. Sudden death is common in areas where community water supplies are Mg deficient (Eisenberg, 1992). Myocardial Mg content is low in people who die of sudden death. Cardiac arrhythmia and coronary artery spasm can be caused by Mg deficiency. Magnesium sulfate reverses endothelin-1 induced vasoconstriction in a number of vascular beds (Kemp *et al.*, 1999). We have demonstrated that Mg reduces vasoconstriction in ciliary arteries (Dettmann *et al.*, 1998) and improves capillary blood flow in glaucoma patients (Gaspar *et al.*, 1995).

4.4. Trigger factors

Patients with a vasospastic diathesis can be spasm free for long periods. It is only under some circumstances that they develop major dysregulation (Fig. 1). While not all factors triggering spasm have been identified, a number of factors are known, such as physical exercise which, in rare cases, may induce spasm with visual symptoms (Imes and Hoyt, 1989; Sacks and Samaha, 1990).

4.4.1. *Emotional stress*

Coronary vasospasm can be caused by emotional stress (Levin *et al.*, 1998; Bashour *et al.*, 1983; Kovacs *et al.*, 1996). This has, for example,

been observed during "killer dreams" (Parmar and Luque-Coqui, 1998). We have described the influence of emotional stress on ocular vasospasm in detail elsewhere (Flammer, 1998a,b). In brief, we observed infarctions of the retina or the optic nerve head after severe emotional stress in patients predisposed to vasospasm.

4.4.2. *Coldness*

Coldness is well recognized to induce spasm in predisposed patients (Edwards *et al.*, 1999), and for this reason cold provocation is used as a standard test for diagnosis of a vasospastic syndrome (Mahler *et al.*, 1989). Immersion of a hand into cold water induces a marked increase of endothelin-1 (Fyhrquist *et al.*, 1990; Zamora *et al.*, 1990). We have observed deterioration of visual fields in vasospastic patients after cold provocation (Guthauser *et al.*, 1988). It should be stressed, however, that some vasospastic patients do not respond with spasm to cold although they do have spasm under emotional stress.

4.4.3. *Migraine*

The relationship between vasospastic syndrome and migraine is quite complex. The two entities should not be confused. On average, patients with vasospasm suffer slightly more from migraine, and vice versa. Migraine, however, can also trigger local vasospasm in the brain and, albeit less frequently, in other organs including the retina. In migraine with aura, cerebral blood flow is decreased in the brain, usually in an area located posteriorly in one hemisphere (Sakai, 1995). The low flow precedes pain and may rapidly increase in size to affect larger parts of the brain (Friberg *et al.*, 1994). There is a close temporal and functional correlation between the neurological deficits of the aura and the localization of the cerebral blood flow changes. Generally, aura symptoms remit within one hour, but the brain tissue hypoperfusion persists for several hours with a considerable overlap into the succeeding headache phase. Thus, headache may not be initiated by hyperemia in the brain tissue. The hyperemia might partially be due to the release of NO from thrombocytes (Shimomura *et al.*, 1999). Endothelin-1 is increased in the beginning of a migraine attack (Hasselblatt *et al.*, 1999). Plasma levels then quickly decrease to normal or even lower levels (Komatsumoto and Nara, 1995). This might be a further cause for the hyperemia.

Irreversible ischemic lesions after migraine attacks have been described in the heart, in the brain and in the eye. Irreversible vasospastic lesions most probably occur more often in vasospastic patients independently of migraine. In such cases, however, the cause of the ischemia may often not have been detected. In contrast, for patients with a migraine attack, the patient history readily indicates that a spastic infarction might be the cause of the lesion.

Recent findings of an association between migraine and normal-tension glaucoma (Cursiefen *et al.*, 2000) are in agreement with the assumption that vasospasm are a pathogenetic factor for glaucoma (Flammer, 1990). Interestingly, visual field loss resembling the early stage of glaucoma can frequently be observed in subjects with migraine headaches (McKendrick *et al.*, 2000).

4.4.4. *Other factors*

Sometimes severe spasm can be observed in predisposed patients without recognizable trigger factors. We therefore deduce the existence of other, as yet unidentified, trigger factors. It is possible that some foods, or smoking in otherwise non-smoking persons, may trigger spasm. In chronic smokers, however, we found increased blood flow velocities (Kaiser *et al.*, 1997).

5. CLINICAL CONSEQUENCES OF VASOSPASM

In the foregoing the different causes and pathophysiology of vasospasm have been discussed. The clinical effects that such vascular dysregulations can have in many different organs will now be addressed. It is not yet known why such spasm can be so localized and confined to one organ or a small part of an organ. It is also not understood why some organs such as the hands, the heart and the eye are more frequently involved than other organs.

5.1. Vasospasm in hands and feet

The classical vasospastic disorder is the primary Raynaud's phenomenon (Mahler *et al*., 1989). This has been discussed that in the context of the so-called primary vasospastic syndrome. More severe symptoms can be observed in the so-called Raynaud's disease occurring in patients with autoimmune diseases, as described in the context of the secondary vasospastic syndrome. It is known that patients with Raynaud's phenomenon have an increased level of endothelin-1 which increases further after cold provocation (Zamora *et al*., 1990). The lower limbs can also be involved (Huygens, 1975), although vasospasm in the legs and feet seem to occur less often. Interestingly, endothelin-1 plasma levels do not change during cold provocation in non-responders or responders (Hollo *et al*., 1998), but an impaired production of prostaglandin I2 and an imbalance between prostaglandine I2 and thromboxane A2 can be observed (Sakamoto *et al*., 1999).

5.2. Heart

The coronary vessels appear to be more often involved in vasospasm than other vessels (Mohri *et al*., 1998). However, it may be that spasm in the coronary vessels do not occur more frequently but are rather more commonly diagnosed than spasm in other vascular beds.

5.2.1. *Variant angina*

The variant angina, also called Prinzmetal angina is due to vasospasm (Miller *et al*., 1981). Endothelin-1 is increased in such patients with further elevation during and shortly after the chest pain (Artigou *et al*.,1993). It occurs more often in patients with type-A behavior (Altura, 1980). It has been hypothesized that patients under constant self-induced stress have increased plasma free fatty acids levels. This in turn reduces the level of free ionized Mg in the blood (see Section 4.3). Activation of protein kinase C, which inhibits endothelial NO formation, by endothelin-1 and prostaglandin F2 alpha has also been suggested (Kanashiro *et al*., 2000).

Interestingly, there is racial heterogeneity in coronary artery vasomotor reactivity. Japanese patients appear to have a higher incidence of inducible spasm than Caucasians (Beltrame *et al*., 1999). This may explain why normal tension glaucoma occurs more frequently in the Japanese population.

Myocardial ischemia can be silent (so-called silent myocardial ischemia) (Waldmann *et al*., 1996). This can occur in patients without any coronary arteriosclerosis (Rowe, 1991). We have observed a marked prevalence of silent myocardial ischemia in patients with glaucoma (Waldmann *et al*., 1996).

5.2.2. *Myocardial infarction*

The vast majority of myocardial infarctions occur in patients with arteriosclerotic lesions. Less frequently, myocardial infarctions occur in patients without any detectable arteriosclerosis. These infarctions are due to vasospasm (Lip *et al*., 1998) which could explain their occurrance even in children (Hosoi *et al*., 1997; Perry *et al*., 1997) and young adults (Duvernoy *et al*., 1998). Thrombosis can superimpose a coronary spasm (Sganzerla *et al*., 1999). In the majority of patients with myocardial infarctions, arteriosclerotic changes in combination with some vascular dysregulation may lead to the eventual vessel obstruction. These dysregulations might be very local. Some patients relate however, that they had very cold hands a few hours before the onset of chest pain.

5.3. Brain

Already in 1984, different aspects of vasospasm in the brain were reviewed (Voth and Glees, 1984). With the exception of findings that NO and endothelin-1 play a major role, little progress on vasospasm in the brain has been made. The brain seems to be less involved in spasm than other organs. The reasons for this are not known. It may be due to the fact that the brain has an efficient autoregulation, and that the blood-brain barrier protects the smooth muscle cells and the pericytes from water-soluble circulating hormones such as endothelin-1 or angiotensin-II.

Spasm have been extensively described and studied in the context of subarachnoidal hemorrhage (see Section 3.3.1), a condition in which endothelin-1 in the CSF is increased.

Cerebral vasospasm has also been described in the context of migraine (Skyhoj-Olsen, 1990). Cerebral blood flow is decreased markedly during the so-called aura (see Section 4.4.3). In rare extreme situations the vasoconstriction may lead to a cerebral infarction (Sanin and Mathew, 1993), also called migraineous stroke. Migraine can also trigger vasoconstrictions in other parts of the body. It is well known that some patients with migraine suffer from very cold hand before and during the attack. Ocular ischemic lesions during migraine attacks will be discussed later. Migraineous patients suffer more often from a primary vasospastic syndrome than the average population.

Finally cerebral vasospasm are known in relation to preeclampsia (see Section 3.1.6), systemic hypertension and AIDS (see Section 3.2.2).

5.4. Ear

Relatively little is known about vasospastic disorders in the ear. Either the ear is less involved or there is just less information available due to the relative inaccessibility of the ear. Nevertheless, migraine can be a cause of sudden hearing loss (Viirre and Baloh, 1996). Fluctuating hearing losses in children have been interpreted to indicate migraine equivalents (Bernard and Stenstrom, 1988). Benign positional vertigo might also be due to vasospasm (Ishiyama *et al.*, 2000). Interestingly, the ocular findings observed in patients with sudden deafness are similar to those in the primary vasospastic syndrome (Erb *et al.*, 1996). Moreover, a large number of patients with a vasospastic normal tension glaucoma can be found to have tinnitus or hearing problems in their patient history.

5.5. Gastrointestinal tract

Vasospasm may induce mesenteric or abdominal angina (Bassiouny, 1997). Drugs such as amphetamine (Johnson and Berenson, 1991) or ergotamine (Greene *et al.*, 1977; Rogers and Mansberger, 1989) can lead to gastrointestinal ischemia. Non-occlusive ischemic colitis secondary to hemorrhagic shock has been described (Byrd *et al.*, 1987). This is interesting because optic nerve ischemia after hemorrhagic shock is frequently observed in vasospastic patients.

5.6. Pulmonary hypertension

Pulmonary hypertension can occur as a primary disease or secondary, following cardiac and pulmonary diseases. In some clinical cases as well as in various models of pulmonary hypertension, endothelin-1 is elevated or its converting enzyme activity is altered, suggesting that endothelin-1 plays an active role in both arteriolar vasoconstriction and occlusion (Veyssier-Belot and Cacoub, 1999). Whilst treatment with calcium channel blockers, prostacyclin analogues and nitric oxide inhalation seems to be beneficial, therapy with endothelin-1 antagonists still has to be considered with caution. Endothelin antagonists lead to pulmonary vasodilatation, but this effect is associated with a reduction in systemic blood pressure and a reduction in arterial oxygen saturation (Prendergast *et al.*, 1999; Williamson *et al.*, 2000). The disturbed balance of release and clearance of endothelin-1 can be improved by epoprostenol (Langleben *et al.*, 1999). In hypoxia-induced pulmonary hypertension, gene transfer of prepro-calcitonin gene-related peptide significantly lowered pulmonary vascular resistance (Champion *et al.*, 2000).

6. INVOLVEMENT OF THE EYE

For ophthalmologists the involvement of the eye in vasospastic disorders is of particular interest. Vasospasm can occur in different parts of the eye and thereby contribute to the pathogenesis of many different eye diseases.

6.1. History

In 1862 Raynaud wrote his thesis on local ischemia in the hands (Raynaud, 1862). In 1895 Oliver and Schaefer postulated that the vasoconstriction might be due to a local factor inducing

the vascular smooth muscle cells to constrict (Oliver and Schäfer, 1895). In 1910 Blessing and Hamburger described retinal angiospasm during a migraine (Blessig and Amburger, 1910). In 1939 Lisch described functional vascular dysregulations of the eye, and even then recognized a relationship with a dysregulation of the finger capillaries (Lisch, 1939). In 1948 Traquair observed spasm in the central retinal artery (Traquair, 1948). Incidentally, at that time the visual symptoms of Adolf Hitler were interpreted by his physician as being of a vasospastic origin (Cogan, 1995).

In 1986 we described an involvement of the eye in the primary vasospastic syndrome (Gasser *et al.*, 1986). One year later we described the assumption that vasospasm might be involved in the pathogenesis of glaucomatous damage (Flammer *et al.*, 1987) and discussed the potential role of calcium channel blockers to treat this condition (Flammer and Guthauser, 1987). At that time it was difficult to measure ocular blood flow in humans, and our suppositions therefore were mainly based on the quantitative relationship between visual function and peripheral blood flow (Guthauser *et al.*, 1988).

6.2. Why is the eye frequently involved?

The circulation of the eye is quite distinctive. Whereas the retina shares many characteristics with the brain, the choroid has more in common with the coronary or finger vessels. The optic nerve head also has quite unique properties. For example, although it has a blood brain barrier, vasoactive substances can diffuse from the choroid into the optic nerve head. These aspects of ocular perfusion have been reviewed previously (Flammer and Orgül, 1998). The special and unique situation of the eye explains why the eye, and especially the choroid, is notably prone to vasospasm (Gasser *et al.*, 1990; Flammer *et al.*, 1996; Prünte-Glowazki and Flammer, 1991). It also explains the involvement of the optic nerve head.

6.3. The ocular vasospastic syndrome

We introduced the term "ocular vasospastic syndrome" to describe involvement of the eye in the vasospastic syndrome, especially in the primary vasospastic syndrome. It is characterized by a mostly diffuse visual field damage, although visual acuity is normal. An ocular vasospastic syndrome can occur in children (Kaiser *et al.*, 1993) and young adults (Flammer, 1993). It should not be confused with functional visual loss (Clarke *et al.*, 1996).

The best way to recognize diffuse visual field defects is by representation of the perimetric result with a "Bebie-curve" (Bebie *et al.*, 1989) (Fig. 5). A diffuse component, as portrayed by a parallel shift of the curve, is very characteristic for a vascular dysregulation. Such a diffuse component can be combined with a local defect. Similar diffuse visual field defects also occur in patients with cataract and in young patients with very high IOP. Both situations can be easily excluded clinically. A marked temporal fluctuation points

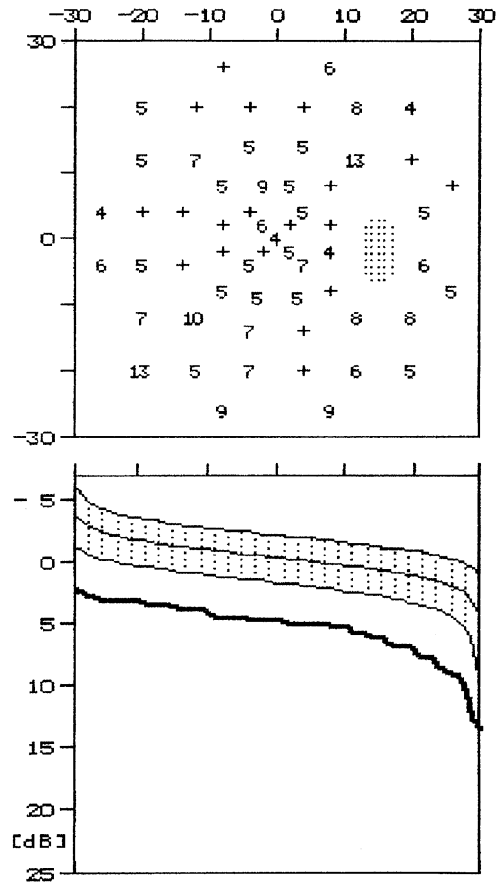

Fig. 5. Typical diffuse visual-field damage in a patient with ocular vasospasm. Upper panel: Numerical grid. Lower panel: Bebie-curve.

further toward a vascular dysregulation. If the etiology of such a diffuse damage remains unclear, a treatment test can facilitate the correct diagnosis. If the visual field defect disappears or improves after short-term treatment with a calcium channel blocker, the diagnosis of a spastic syndrome is definitive (Guthauser *et al.*, 1988). A normal visual field does not exclude the involvement of the eye under other circumstances such as in cold weather or when under emotional stress. If suspicions remain, a cold provocation test can assist in diagnosis. Subsequent to immersion of one hand in cold water, the visual fields of some patients with vasospasm deteriorate. The ocular vasospastic syndrome is normally not recognized by either the patient or the ophthalmologist. This is not a major problem as the syndrome is mostly harmless. However, if the patient has symptoms, or if the optic nerve head turns pale or even starts to excavate, a clinical evaluation is warranted.

The visual dysfunction seems to be due to a reduced circulation in the choroid (Prünte and Flammer, 1989, 1996) and potentially also in the optic nerve head. Normally, the ocular vasospastic syndrome is reversible and does not need treatment if there are no coexistent complications (see also Section 2.2). However, it is a risk factor for a number of diseases which are discussed in subsequent sections.

7. OCULAR DISEASES IN WHICH VASOSPASM MIGHT BE INVOLVED

Most of the ocular diseases we know are characterized phenomenologically. In terms of pathophysiology, different mechanisms and different factors may underlie a similar disease. Furthermore, since diseases are often multi-factorial, one pathogenic factor such as vasospasm may just play a role in concert with many other factors. The following discussion considers eye diseases for which there is some published information to support a pathogenetic involvement of vasospasm.

7.1. Alteration of conjunctival vessels

Although the conjunctival vessels are easily accessible to the ophthalmologist there is surprisingly little literature information about their involvement in the vasospastic syndrome. Nevertheless, vascular abnormalities can be visualized in the conjunctiva, especially in patients with vascular dysregulation (Orgül and Flammer, 1995; Stubiger *et al.*, 1997) (Fig. 2). We are currently investigating a large number of normal individuals and patients to determine the sensitivity and the specificity of such vascular alterations.

7.2. Corneal edema

In rare patients coldness can induce a corneal edema. It is interesting that a transient corneal opacity occurs in patients with Raynaud's disease (McWhae and Andrews, 1991) and is accompanied by changes in the conjunctival vessels.

7.3. Retinal arterial occlusions

Retinal arterial occlusions normally occur in older patients with arteriosclerosis. Sometimes occlusions occur in young patients who have neither risk factors nor any signs of arteriosclerosis (Katz, 1986). Such patients nearly always have a vasospastic syndrome, and the occlusions generally occur after major emotional stress (Flammer, 1998a,b). Some of these patients suffer from a so-called Susac syndrome. We have postulated that the Susac syndrome is a special manifestation of the primary vasospastic syndrome. The cilioretinal arteries seem to be especially involved in the vasospastic syndrome, most notably in patients with anorexia nervosa (see Section 3.3.6).

Furthermore, the resistivity measured with CDI in otherwise healthy subjects with vascular dysregulation is inversely correlated to systemic blood pressure (Gherghel *et al.*, 1999).

7.4. Retinal vein occlusions

The classical risk factors for retinal vein occlusions are systemic hypertension and glaucoma. In general, risk factors for arteriosclerosis also appear to be risk factors for vein occlusions.

However, vein occlusions are observed in patients who have neither glaucoma, nor risk factors or signs of arteriosclerosis. Activated protein C resistance may play an additional role in some patients (Guven *et al.*, 1999). We observed

that a number of patients with a vein occlusion have primary vasospastic syndrome (Messerli and Flammer, 1996). That vein occlusions in young adults occur more often in winter is consistent with the assumption that vasospasm play a role (Lavin and Dhillon, 1987). Vein occlusions have also been observed in patients with secondary vasospasm, for example in patients with AIDS (see Section 3.2.2) or colitis ulcerosa (Doi *et al.*, 1999). Interestingly, endothelin-1 concentrations are increased in patients with retinal vein occlusions (Iannaccone *et al.*, 1998). The injection of endothelin-1 intravitreally can induce a transient, complete obstruction of retinal vessels combined with an increase in choroidal blood flow (Sato *et al.*, 1995).

Retinal vein occlusion in the context of migraine has also been described (Friedman, 1951). In any individual case it is difficult to know whether there is a causal relationship or an association by chance.

Combined cilioretinal artery and central retinal vein occlusion (Berler, 1994; Keyser *et al.*, 1994) can be observed in young vasospastic patients. Such a combined occlusion has been described in an eight year old girl (Leys, 1992). These patients seem to have a favorable prognosis (Schatz *et al.*, 1991).

Young patients with central vein occlusion often also have disc edema (Fong *et al.*, 1992). There is no clear discrimination from the so-called papillophlebitis (Ellenberger and Messner, 1978), which also occurs mostly in young vasospastic women (Serdaru *et al.*, 1984) and has a good prognosis.

7.5. Choroidal ischemia

The choroid is highly perfused and this perfusion is regulated by many factors. Vascular dysregulation may occur quite often but is rarely detected (Flammer and Guthauser, 1987). Reduced perfusion in the choroid is most probably the cause of the reversible diffuse visual field damage in the so-called ocular vasospastic syndrome (Gasser and Flammer, 1987). A dysregulation, however, may also be quite local and then produce different clinical pictures. We have observed a forty year old vasospastic lady who developed a choroidal infarction during major emotional stress (Fig. 4). We have also observed choroidal vascular dysregulations in patients with central serous chorioretinopathy (Prünte and Flammer, 1996).

7.6. Amaurosis fugax

Amaurosis fugax, or transient monocular blindness, is caused by an abrupt temporary reduction in blood flow to one eye. The loss of vision is sudden, usually lasting seconds or minutes. Blindness is complete, although sometimes limited to a sector of the field of vision. Attacks can be single or multiple. In most patients the prognosis for retinal recovery is good, but in a few cases retinal infarction occurs (Tippin *et al.*, 1989), even in adolescents and young adults. There are a number of causes for amaurosis fugax, including thromboemboli. A number of authors, however, have suggested that vasospasm might be an important cause (Burger *et al.*, 1991; Bernard and Bennett, 1999). Amaurosis fugax has also been associated with migraine. Vasospastic amaurosis fugax were observed in patients with autoimmune diseases (Ploner *et al.*, 1995) and after metamphetamine inhalation (Shaw *et al.*, 1985). A positive response to calcium channel blocker therapy is a further indication that vasospasm can be involved in amaurosis fugax (Winterkorn *et al.*, 1993).

7.7. Anterior ischemic optic neuropathy

The anterior ischemic optic neuropathy (AION) has a similar risk profile as that for cerebral vascular insults — in other words, it is mostly due to arteriosclerosis. However, it is common to observe AION in young patients without arteriosclerosis. Such patients normally suffer from a vasospastic syndrome (with an increased baseline level of endothelin-1) and the acute events occur mostly after a major emotional stress (Kaiser *et al.*, 1996a,b). AION can also occur in the context of migraine (Katz, 1985; Weinstein and Feman, 1982; Katz and Bamford, 1985). The AION in young vasospastic patients have a relatively good spontaneous recovery (Barrett *et al.*, 1992) but can recur (Hamed *et al.*, 1988). Bilateral AION has been observed secondary to acute ergotism.

Giant cell arteritis (see Section 3.1.2) is another cause of AION. The reduction of blood flow in the eye is often greater than one would expect from the arteritis itself, and the choroid is more involved than the retina (Valmaggia *et al.*, 1999) (Fig. 6). This led us to assume that a secondary vasospastic syndrome may play a major role (Lübeck *et al.*, 1998). Indeed, in these patients we have found increased endothelin-1 plasma levels which might account for the reduced ocular perfusion (unpublished data). The elevated endothelin-1 levels can also explain why on the one hand, the visual loss can progress despite high dosage intravenous steroid therapy (Cornblath and Eggenberger, 1997) and why, on the other hand, the visual field defects often recover later (Lipton *et al.*, 1985; Postel and Pollock, 1993). Sensorineural hearing loss has also been observed in such patients (Hausch and Harrington, 1998).

7.8. Miscellaneous

Vasospasm contributes to the damage after hemorrhages (Maeda *et al.*, 1997). Optic disc hemorrhages precede retinal nerve fiber damage (Airaksinen *et al.*, 1981). By analogy to what is known about the hemorrhages in the brain, we postulated that hemorrhages in the nerve fiber layer may induce spasm and therefore secondary ischemia (see Section 3.3.1) (Orgül and Flammer, 1994).

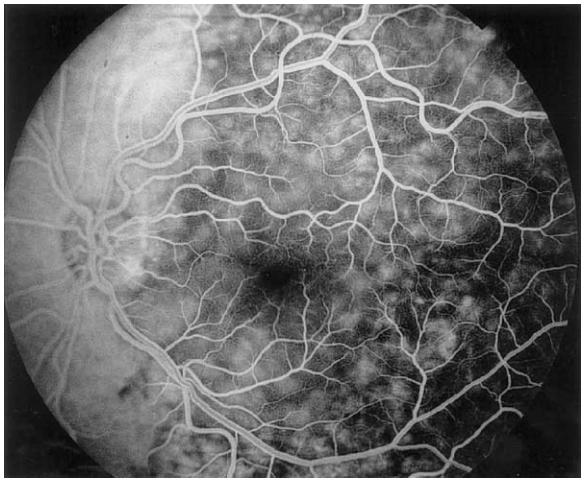

Fig. 6. Markedly delayed chorioidal filling in a patient with giant cell arteritis.

The vasoconstrictions and ischemia observed in the choroid, the optic nerve head and in the retina in the Purtscher's retinopathy also seem to be due, at least in part, to vasospasm (Gomez-Ulla *et al.*, 1996). Chronic pain in both the eye and the orbit can occur in patients with vasospasm. Light-induced ocular pain in a patient with Raynaud's phenomenon was described (Safran and Boschi, 1997). A transient orbital ischemic syndrome occurring mostly in young women may also be due to a vascular dysregulation (Chan *et al.*, 1999). Finally, a fourth nerve palsy has been observed as aura of a migraine (Wong and Sharpe, 1996).

8. THE INVOLVEMENT OF SEVERAL ORGANS IN THE SAME PATIENT

We have discussed the fact that vasospasm can occur in different organs. For unknown reasons some organs are more involved than others. Nevertheless, it is not surprising that patients with a vasospastic syndrome may have clinical manifestations in several organs concurrently or sequentially. We have observed a number of patients with ocular vasospasm and simultaneous hearing loss or tinnitus. Further, we have known patients with severe ocular vasospasm who either died young of a myocardial infarction, or who had relatives dying at young ages of myocardial infarction. Retinal spasm has been observed in patients with concurrent unstable primary angina (Baksi, 1984). A young woman has been described as having branch retinal artery occlusions and a morbus Ménière (Recupero *et al.*, 1998). Another young lady was reported to be suffering from migraine, Raynaud's syndrome and myocardial infarction (Lüthi *et al.*, 1984). The classical combination occurs in the so-called Susac syndrome (Susac *et al.*, 1979), a microangiopathy of retina, cochlea and brain that leads to visual symptoms, hearing loss and neurological symptoms. We hypothesize that the Susac syndrome is a special manifestation of the vasospastic syndrome, as these patients usually present with a history of cold hands, low blood pressure and migraine. The clinical examination shows alterations of the conjunctival vessels, a prolonged stop of flow in

the nailfold capillary microscopy after cooling, an increased resistivity in the orbital vessels on color Doppler imaging and an elevated plasma level of endothelin-1 (unpublished data).

Silent myocardial ischemia can be observed in up to 50% of the patients with normal tension glaucoma (Waldmann *et al*., 1996). It is important to note that these patients have normal ECG when measured during physical exercise. Macular capillary hemodynamics are changed in patients with Raynaud's phenomenon (Salmenson *et al*., 1992). These above mentioned examples demonstrate that several organs might be involved in the spastic syndrome at any given time, and additional changes in some other organs may simply not be detected.

Assumptions of ocular vascular dysregulation were originally based on the correlation between visual function and peripheral blood flow (Guthauser *et al*., 1988). In the meantime we have been able to demonstrate that a relationship between peripheral and ocular circulation exists. There are relationships between corneal temperature and finger temperature (Girardin *et al*., 1999), between optic nerve head blood flow and finger blood flow, between blood flow in the ophthalmic artery and blood flow in the nailfold capillaries (Gasser *et al*., 1999), and between blood flow in the retro bulbar vessels and optic disc blood flow (Bohdanecka *et al*., 1999).

9. VASOSPASM AND GLAUCOMA

In addition to elevated IOP, the vasospastic syndrome is now an established major risk factor for glaucoma (Flammer, 1994; O'Brien, 1998). The role of vasospasm in the pathogenesis of glaucoma has been reviewed extensively elsewhere (Flammer, 1996; Flammer *et al*., 1999). Vascular dysregulations interfere with autoregulation and render the eye more sensitive both to IOP increase and to blood pressure decrease (Flammer *et al*., 1999). The dysregulation also leads often to systemic hypotension. Reduced diastolic perfusion pressure has been shown to be an important risk factor for primary open-angle glaucoma (Bonomi *et al*., 2000). The vascular dysregulation may partially be due to dysfunction of the autonomic nervous system. Heart-rate variability analysis of patients with normal-tension glaucoma indicates a disturbance of the circadian rhythm (Kashiwagi *et al*., 2000). The involvement of vascular dysregulations in this subgroup of glaucoma (Flammer, 1992; Broadway and Drance, 1998; Prünte and Flammer, 1997) explains the observation that glaucomatous damage occurs despite normal IOP. There is, however, no abrupt change in pathophysiology between normal-tension glaucoma and high-tension glaucoma, but the probability of finding vascular abnormalities is higher if damage occurs at lower IOP. Indeed, the involvement of acral vasospasm is higher in normal-tension glaucoma than in high-tension glaucoma (Gasser and Flammer, 1991). Females, known to more frequently have vascular dysregulations than males, also suffer optic nerve head damage more frequently even their IOP is, on average, the same as in males (Orgül *et al*., 1995). Vascular dysregulation may also involve the veins and leads to barrier dysfunction. Glaucoma patients have increased incidents of venous "thrombosis" and disc hemorrhages. The dysregulation interferes with the autoregulation, and consequently, the variation of ocular perfusion pressure leads to variation of ocular perfusion. Visual fields of glaucoma patients fluctuate markedly in relation to IOP (Flammer, 1985). Glaucoma patients also have elevated endothelin-1 plasma levels (Kaiser *et al*., 1995; Flammer, 1997a,b). Interestingly, endothelin-1 levels in plasma and aqueous humor of normal tension glaucoma patients are higher than those in patients with chronic open angle glaucoma (Cellini and Caramazza, 1999). In animal experiments, locally applied endothelin-1 leads to an increase in intraocular glutamate concentration (Kim *et al*., 2000). Elevated vitreous glutamate levels are also seen in experimental ischemia-reperfusion (Kageyama *et al*., 2000). It has been shown that the vitreous body of glaucoma patients contains increased levels of glutamate (Dreyer *et al*., 1996).

The lack of an adequate system to maintain blood flow independent of IOP and blood pressure fluctuation also leads to reperfusion damage. Such reperfusion damage leads to a marked increase in free oxygen radicals which damage DNA and the cell membrane as well as mitochondrial

membranes. This initiates a subsequent cascade of events that eventually lead to a caspase-mediated digestion of retinal ganglial cells with their axons as well as glial cells in the optic nerve. A deeper understanding of the (to date) poorly explored genetic pathways of apoptosis is desirable.

10. THERAPY

Since the clinical impact of vascular dysregulation has only really been appreciated within the last few years, therapeutic research in this field has only recently started.

In the prevention of cerebral vasospasm-induced hemorrhage, intrathecal sodium nitroprusside (Vajkoczy *et al.*, 2000) and urokinase cisternal irrigation therapy (Sasaki *et al.*, 2000) seem to be beneficial. In intractable migraine, treatment with verapamil is promising as it appears to reverse vasospasm of the major cerebral arteries (Ng *et al.*, 2000).

Intracoronary infusion of nitroglycerine and verapamil relieves coronary spasm after coronary artery bypass grafting (Caputo *et al.*, 1999). Some authors suggest intraluminal injection of vasodilators such as calcium channel blocker (CCBs) in combination with nitroglycerin whenever there is a high suspicion of vasospasm in arterial grafts (He *et al.*, 2000), or even topical pre-treatment of artery grafts with glyceryl trinitrate and papaverine (Chavanon *et al.*, 1999).

Antivasospastic treatment with CCBs in glaucoma patients seems to be helpful although its usefulness is not yet firmly established (Yamamoto *et al.*, 1998; Tomita *et al.*, 1999). Short-term studies indicate that CCBs diminish the effect of increased levels of endothelin-1 on ocular perfusion (Strenn *et al.*, 1998; Daugeliene *et al.*, 1999) and improve visual field defects (Flammer and Guthauser, 1987; Gasser and Flammer, 1990; Gaspar *et al.*, 1994). That the same effect can be achieved by CO_2 inhalation (Niwa *et al.*, 2000) indicates that the visual function improvements are in fact due to vasodilatation. CCBs reduce the vasoconstrictive effect of endothelin-1 in vitro (Meyer *et al.*, 1995; Lang *et al.*, 1997). Furthermore, CCBs are used to treat the so-called ocular ischemic syndrome (Winterkorn and Beckman, 1995) and the vasospastic amaurosis fugax (Winterkorn *et al.*, 1993). The role of CCBs in glaucoma has been reviewed elsewhere (Flammer, 1997a,b). Possible side effects of CCB treatment are dose dependent and usually associated with higher doses. Nevertheless, the benefit as well as the possible long-term adverse effects of CCBs should be closely monitored.

The beta-blocker Betaxolol has calcium antagonistic properties (Melena *et al.*, 1999). In severe vasospastic children low-dosage propanolol seems to be beneficial (Kaiser *et al.*, 1993). Magnesium, the physiological calcium antagonist, modulates endothelin-1-induced vasoconstriction (Dettmann *et al.*, 1998) and improves peripheral circulation in vasospastic patients (Gaspar *et al.*, 1995). Mg also reverses vasoconstrictions after subarachnoidal hemorrhages (Ram *et al.*, 1991). Dipyridamol reduces the vasoconstrictive effect of endothelin-1 (Meyer *et al.*, 1996) and improves the ocular circulation of vasospastic patients (Kaiser *et al.*, 1996a,b). Fish oil improves circulation in patients with Raynaud's phenomenon (DiGiacomo *et al.*, 1989), also by inhibiting the endothelin-1 effect (Nitta *et al.*, 1998). Vitamin E improves vasospastic angina by decreasing oxidative stress (Motoyama *et al.*, 1998). A number of herbal drugs such as ginkgo (Ritch, 2000) might also be beneficial.

11. FUTURE DIRECTIONS

The diagnosis of vasospasm is mainly based upon patient's history, capillary microscopy and angiography. We need further diagnostic tools with higher sensitivity and specificity. An elevated endothelin-1 plasma level is a sensitive indicator, but unfortunately not specific for a vasospastic syndrome. The diagnostic value of endothelin-1 as well as that of NO, prostaglandins and other vasoactive substances must be further evaluated.

The pathophysiology of vascular dysregulation is still poorly understood. Vasospasm are the result of a complex and only partly disclosed interaction of the endothelium, perivascular nerves and a variety of mediators. In addition to vasoactive substances such as endothelin-1 and NO, protein kinases are also suspected of being involved in triggering and maintaining vasospasm

(Zubkov *et al*., 2000). The role of some cell adhesion molecules (e.g. P-selectin or intracellular adhesion molecule-1 (ICAM-1)) in the development of reperfusion injury is not yet clear (Tsujikawa *et al*., 1999). Little is known about the effect of a number of vasoactive substances (e.g. calcitonin gene-related peptide, urotensin) on the genesis and perpetuation of vasospasm. The influence of genetics is also unclear.

Treatment modalities are at the moment sparse, and we currently lack the ideal anti-vasospastic drug. But research on a variety of therapeutic strategies has started. Drugs such as CCBs and nitroglycerin (Ito *et al*., 2000), traditionally used for other indications, may reduce vasospasm. Interestingly, the CCB Lomerizine significantly reduces glutamate-induced neurotoxicity in experimental studies (Toriu *et al*., 2000). In animal experiments, the glutamate antagonists memantine and dizocilpine successfully block the toxic effect of glutamate on retinal ganglion cells (Gu *et al*., 2000), and doxorubicine is a successful inhibitor of endothelin-1 induced cerebral vasospasm (Mostafa *et al*., 2000). Antioxidants such as ebselen may have a beneficial role in the therapy of posthemorrhagic vasospasm (Handa *et al*., 2000). Antioxidants also prevent smooth muscle cells from intracellular calcium overload resulting from low serum Mg concentrations (Li *et al*., 2000). Endothelin-1 antagonists will soon become available for clinical use, but treatment during pregnancy might induce neural malformation. Unfortunately, vasospasm is more common in young females.

Gene-transfer is another promising strategy. Although this is a very young experimental field, new benchmarks have already been set through the successful transfer of prepro-calcitonin gene-related peptide (Toyoda *et al*., 2000) and recombinant endothelial nitric oxide synthase gene (Stoodley *et al*., 2000).

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