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What Is the Link Between Vascular Dysregulation and Glaucoma?

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Abstract. The need of blood flow to different organs varies rapidly over time which is why there is sophisticated local regulation of blood flow. The term dysregulation simply means that blood flow is not properly adapted to this need. Dysregulative mechanisms can lead to an over- or underperfusion. A steady overperfusion may be less critical for long-term damage. A constant underperfusion, however, can lead to some tissue atrophy or in extreme situations to infarction. Unstable perfusion (underperfusion followed by reperfusion) leads to oxidative stress. There are a number of causes that lead to local or systemic vascular dysregulation. Systemic dysregulation can be primary or secondary of nature. A secondary dysregulation is due to other autoimmune diseases such as rheumatoid arthritis, giant cell arteritis, systemic lupus erythematodes, multiple sclerosis, colitis ulcerosa, or Crohns disease. Patients with a secondary vascular dysregulation normally have a high level of circulating endothelin-1 (ET-1). This increased level of ET-1 leads to a reduction of blood flow both in the choroid and the optic nerve head but has little influence on autoregulation. In contrast, primary vascular dysregulation has little influence on baseline ocular blood flow but interferes with autoregulation. This, in turn, leads to unstable oxygen supply, which seems to be a relevant component in the pathogenesis of glaucomatous optic neuropathy. (**Surv Ophthalmol 52**:S144–S154, 2007.

Key words. drug sensitivity • endothelin-1 • feeling of thirst • glaucoma • PVD • sleep behavior • SVD • vascular dysregulation

The main function of blood flow is to ensure adequate supply of oxygen and nutrients to the tissue in our body. The overall blood flow is equal to the cardiac output, and its distribution to different organs is regulated by the relative local resistance. The regulation of ocular blood flow (OBF) is complex.[30] It adapts to changing metabolic needs during changing visual function, compensates for varying perfusion pressure, and maintains the temperature at the back of the eye constant.[15] Many systems, such as endothelial cell layer, circulating hormones, and the autonomic nervous system are, among others, involved in this regulation. It is obvious that the more complex the regulative system (e.g., in the eye), the more susceptible it is for dysregulation and the more dramatic the potential for damage. Dysregulation of the resistance, in other words, of the blood vessels, denotes an inappropriate local regulation of arteries, veins, and capillaries.[31] As a consequence, local blood supply does not correspond to the local demand. This can imply over- or underperfusion and may result in a heterogeneous flow. Although it is currently less clear what degree of overperfusion is detrimental to the tissue,[80] underperfusion may be harmful and can lead in extreme situations even to infarctions. Thus, more attention is paid to underperfusion. Local reduction of blood flow is either due to an insufficient vasodilatation if needed or due to an inappropriate vasoconstriction (vasospasm). This condition is called *vascular dysregulation* and can occur globally, involving many different organs simultaneously or sequentially. Vascular dysregulation can be classified as primary vascular dysregula-

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tion (PVD) and secondary vascular dysregulation (SVD).[31] This review aims to summarize findings of vascular dysregulation relevant to eye diseases.

Ocular Blood Flow (OBF)

In the following sections we will discuss the regulation of blood flow, in particular, the autoregulation as it is relevant to the pathogenesis of glaucomatous optic neuropathy (GON). In terms of mechanisms, we particularly emphasize the role of the endothelium cell layer, as there are indications that the major cause of primary vascular dysregulation is a vascular endotheliopathy.[16,68,84,94]

REGULATION OF OCULAR BLOOD FLOW

The functions of the regulation of OBF are to adjust to changes in perfusion pressure (autoregulation), to keep the temperature of the back of the eye constant (thermoregulation), and to adapt to neural functions (neurovascular coupling).[50] Moreover, the circulation in the eye is regulated differently in different tissues. The retina is regulated mainly by the endothelial cells and by the neural and glial cells.[115] The choroid is regulated mainly by the autonomic nervous system and circulating hormones.[11,127] The blood flow in the optic nerve head (ONH) is regulated mainly by endothelial cells and circulating hormones.[125]

AUTOREGULATION

Autoregulation is defined as the component of regulation that compensates for variation in perfusion pressure. It functions sufficiently only within a certain range of perfusion pressure.[71,93,113,115,125] Several systems are involved in autoregulation, such as myogenic response, metabolic mechanisms, and endothelial cell function.[32,62,110]

ENDOTHELIUM-DERIVED VASOACTIVE FACTORS (EDVF)

The vascular endothelium is a confluent monolayer of flattened cells that lines the inner surface of the vasculature. The layer is not just a barrier but also an active regulator of vascular tone.[34] Endothelial cells function like a relay-station receiving physical information (e.g., sheer stress), chemical information (e.g., oxygen tension), and biological information (e.g., hormones). All of this information is integrated, giving rise to production and release of endothelial-derived vasoactive factors (EDVFs).[58] The EDVFs work in concert with other systems, such as the autonomic nervous system. The key EDVFs are nitric oxide (NO), endothelin-1 (ET-1), and prostacyclin (PGI2).[49,57,59] There is a basal production of

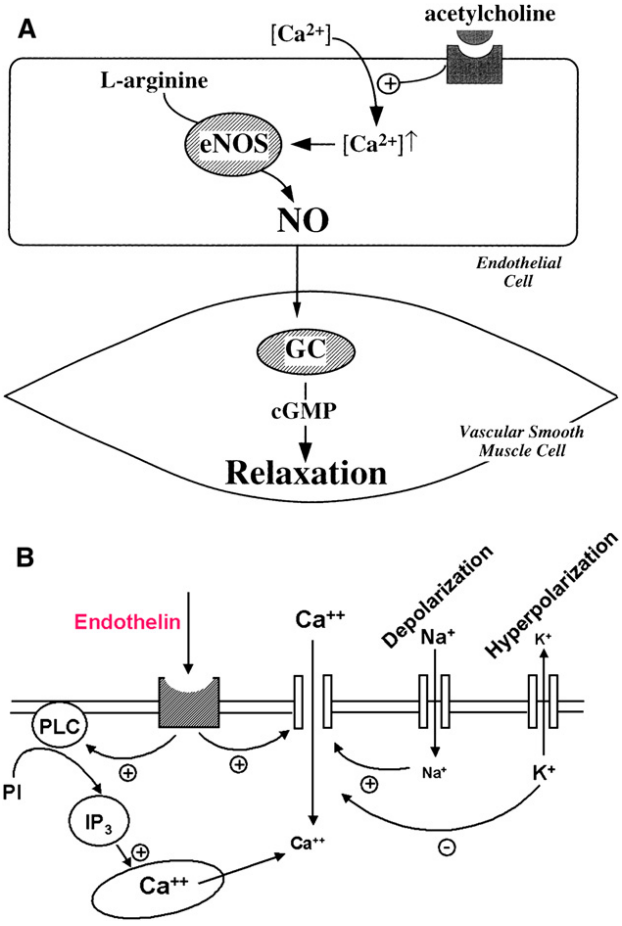

Fig. 1. A: Schematic representation of the nitric oxide synthase/guanylate cyclase pathway in a blood vessel wall. In endothelial cells nitric oxide (NO) is synthesized from L-arginine via the activation of a calcium (Ca^2+)-dependent nitric oxide synthase (NOS). NO production can be inhibited by false L-arginine analogs, such as L-N ^{G}-monomethyl arginine (L-NAME). In vascular smooth muscle cells, NO activates a soluble guanylate cyclase (sGC), which increases 3′5′-cyclic guanylate cyclase (cGMP) leading eventually to a relaxation. Receptor-operated agonists (R), such as acetylcholine (Ach) can stimulate the production of NO. (Reprinted from Haefliger et al[57] with permission of *Progress in Retinal and Eye Research.*) *B:* The calcium channels are regulated in part by both the potential of the cell membrane and the G-proteins. The G-proteins, in turn, are activated by various hormone receptors. (Reprinted with permission from Flammer J, Die Behandlung des Normaldruckglaukoms mit Kalziumantagonisten. Search on Glaucoma 5:3–7, 1997.)

NO; a stimulation of endothelial cells (e.g., with acetylcholine) leads to an additional production of NO. NO diffuses into neighboring cells, including pericytes and smooth muscle cells. NO stimulates the guanylate cyclase, causing an increase in cyclic guanine monophosphate (cGMP) and thereby leading to relaxation of smooth muscle cells and pericytes, which, in turn, leads to vasodilation (Fig. 1).[60,136] The most important vasoconstrictive

factor is ET-1. ET-1 is a 21-amino acid peptide that is secreted mostly abluminally but, to some extent also intraluminally, leading to a certain concentration of ET-1 in the circulating blood. There are two ET receptors, namely, ET-A and ET-B. The stimulation of ET receptors on smooth muscle cells or pericytes increases cytoplasmic calcium, both by influx into the cell, as well as by liberation of calcium from the internal storage. This, in turn, leads to constriction of the vessels (Fig. 1).[87] If the concentration of ET-1 is even higher, it leads to vasospasm.[138]

CIRCULATING HORMONES

Vasoactive molecules are also found in the circulating blood. A clinically important example is angiotensin- I, which is locally converted to angiotensin- II.[86,116,124] In addition, all the EDVFs discussed previously are also partially secreted abluminally, and therefore, act not only locally but also systemically. The effect of circulating molecules depends on the site of action. Serotonin dilates vessels by stimulating S1-receptors on endothelial cells, whereas it constricts vessels when stimulating S2- receptors on smooth muscle cells. In a similar way ET-1 has a slight dilatation effect when stimulating receptors of endothelial cells, but leads to vasoconstriction when it has access to receptors of the smooth muscle cells. Intravenous infusion of ET-1 in young healthy people therefore leads to major reduction of choroidal blood flow (fenestrated capillaries),[130] but does not change the brain circulation. In conditions where the blood–brain barrier is disturbed—for example, in an acute plaque of a multiple sclerosis patient—circulating ET-1 leads to vasoconstriction. As mentioned previously, it also leads to a reduction of blood flow in the choroid even in healthy people. Interestingly, the ONH, although anatomically part of CNS, is not fully protected by barriers: First, there is some diffusion from the surrounding choroid[5,13,25,67,133] and second, the blood vessels in the ONH, originating from the ciliary circulation, have weaker barrier function than the capillaries in other parts of the CNS or the retina.[45,69] This explains why circulating hormones such as angiotensin II or ET-1 have a major impact on ONH circulation[124] that is not present in the retina or in the CNS as long as the vessels are intact.

Vascular Dysregulation

As mentioned previously, a regulation of circulation that is not properly adapted to the local needs is defined as vascular dysregulation. Such a dysregulation can be local (e.g., after rupture of an atherosclerotic plaque) or global. We will now focus on systemic dysregulation, which can be primary or secondary in nature.

PRIMARY VASCULAR DYSREGULATION SYNDROME (PVD SYNDROME)

Subjects with a PVD syndrome have an inborn tendency to respond differently with their vascular system to various stimuli; for this reason the terminology PVD.[31] They also exhibit other differences (e.g., sleep behavior, feeling of thirst, drug sensitivity). Although they can hardly be distinguished from others under baseline conditions, they respond differently to stimuli such as cold, mechanical or psychological stress, and so forth.[10,26,85,135] Among the most prominent pathological reactions are the vasoconstrictions, leading to the previously used term *vasospastic syndrome*.

The PVD syndrome occurs more frequently in women than in men,[109] in Japanese than in whites,[4,91] and in academics than in blue collar workers.[63] The symptoms are normally first manifested in puberty and mitigate with age.[27,70] In women, a marked drop of symptoms is often observed after menopause but can re-exacerbate when women with PVD receive hormonal-replacement therapy,[73] although others did not find such a relation to sex-hormones in patients with Raynaud syndrome.[2] It remains unclear why women suffer more often from PVD than men. Possibly, female hormonal and hereditary factors, such as change of the endocrine function with age, might be related to the higher occurrence of PVD in women.

PVD AND BLOOD PRESSURE

Patients with PVD tend, on average, to have low blood pressure, especially at night and particularly when they are young.[99] Some of them suffer from orthostatic hypotension. The major cause for systemic hypotension in these patients is a reduced reabsorption of sodium in the proximal tubule of the kidneys.[106] In other words, subjects with PVD lose more salt in the kidneys. This abnormal renal sodium handling, which is ET-1 dependent, has also been demonstrated in patients with PVD and normal-tension glaucoma.[105] The nocturnal non-dipping and over-dipping,[100] however, are less a consequence of PVD but rather a manifestation of a dysfunction of the autonomic nervous system.[33] Other indications for a link between endothelial and autonomic nervous system dysfunctions in PVD are a significant increase in ET-1 levels,[96] a blunted blood pressure response, and a reduction in ONH blood flow in response to cold provocation.[41]

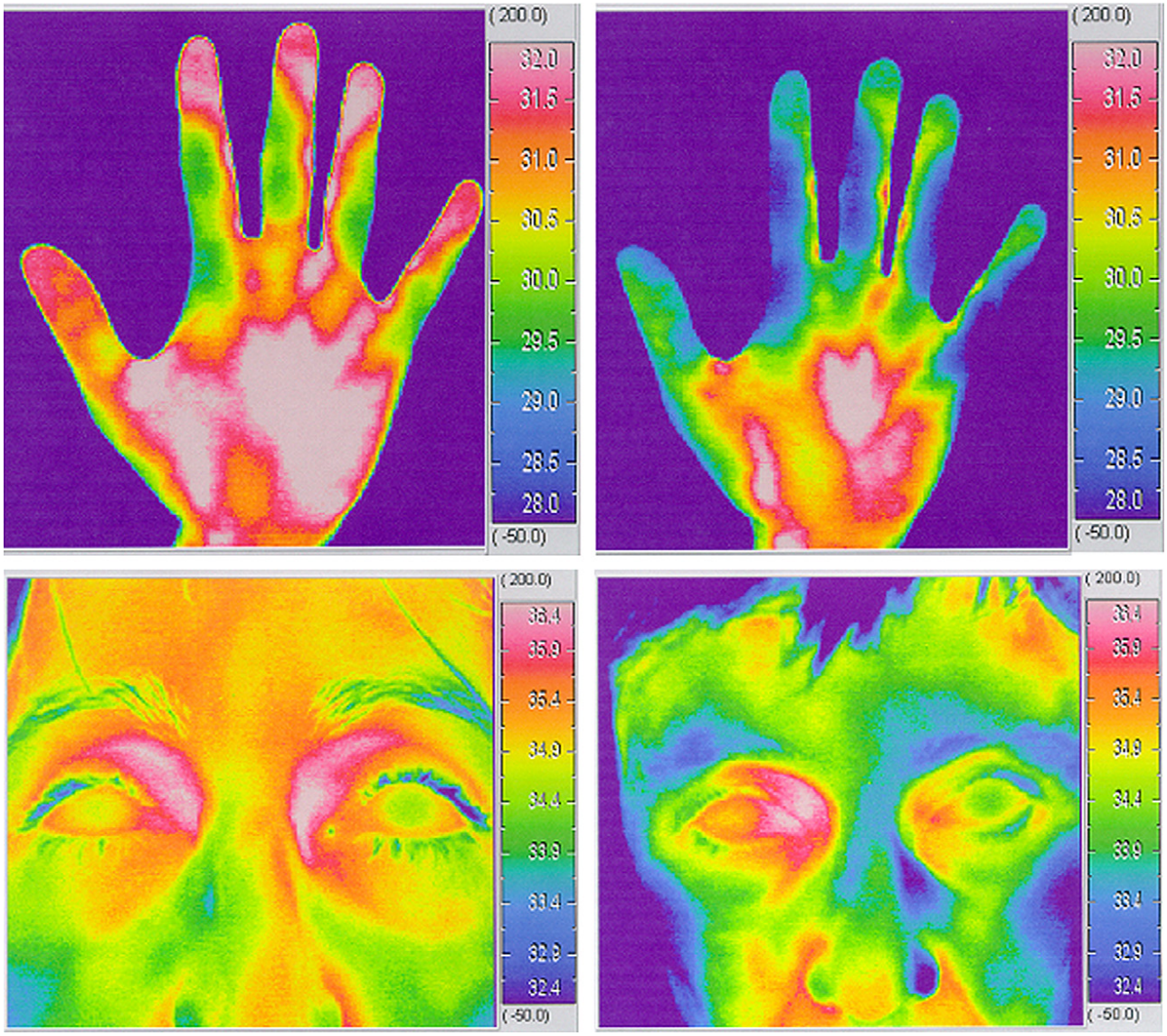

Fig. 2. Thermography. Comparison between a subject without PVD (*left*) and with PVD (*right*) displays a cold face and hand in PVD and a warm picture of a subject without PVD.

PVD AND TEMPERATURE

Cold hands are a leading symptom for PVD;[31] however, patients with cold hands sometimes do not realize their condition, as they are completely used to it. Shaking a patient's hands often gives sufficient information to the doctor. When temperature is measured (e.g., with thermography; Fig. 2),[126] temperature differences are even more striking in the legs.[81] This information, however, can less easily be obtained in daily practice.

PVD AND THIRST

People with PVD, on average, have less desire to drink.[131] This phenomenon can be explained by a mild increase in ET-1 having, via prostaglandin-E_2, an anti-dipsogenic effect in the center of thirst (hypothalamus).[24,129] The average daily intake of fluid, however, is only slightly less than in non-PVD patients.[131] This is due to the fact that these patients drink because they know they need to drink.

PVD AND TRIGGERS

Based on our experience, individuals with PVD, in general, tend to be very particular and diligent. In professional life, they are successful, have often academic degrees, and work often in positions of leadership.[27] However, PVD subjects are sensitive in all respects. They respond more intensively when challenged by cold, or mechanical or psychological stress.[10,26] Although these people are also physically very active, they get cold fast when staying inactive in a cold environment. A mechanical stress, for

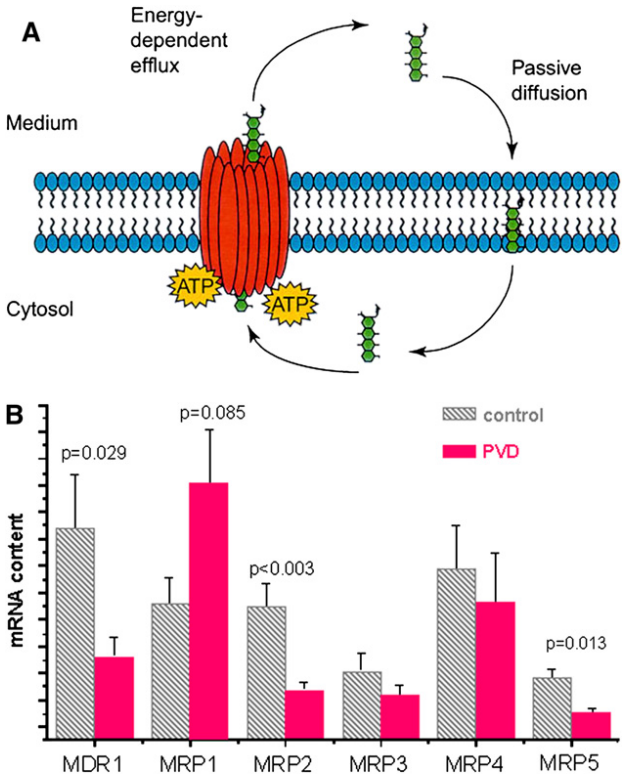

Fig. 3. Drug sensitivity. *A:* Drugs diffuse passively into cells but are pushed out actively by ABC transport proteins. (Reprinted with permission from Johnstone RW et al: Multiple physiological Functions for multidrug transporter L-glycoprotein? Trends Biochem Sci 25:1–6, 2000.) *B:* Gene expression of multidrug resistance (MDR1) and multidrug resistance-associated proteins (MRP isoforms). Mean gene expression of MDR1 and MRP isoform (MRP1 to MRP5) genes in healthy controls and vasospastic persons. Error bars represent the standard error of the mean. Subjects with PVD, although having, on average, the same amount of ABC-transport proteins, reveal large big differences in individual proteins, explaining altered drug sensitivity. (Reprinted from Wunderlich et al[134] with permission of *Molecular Vision.*)

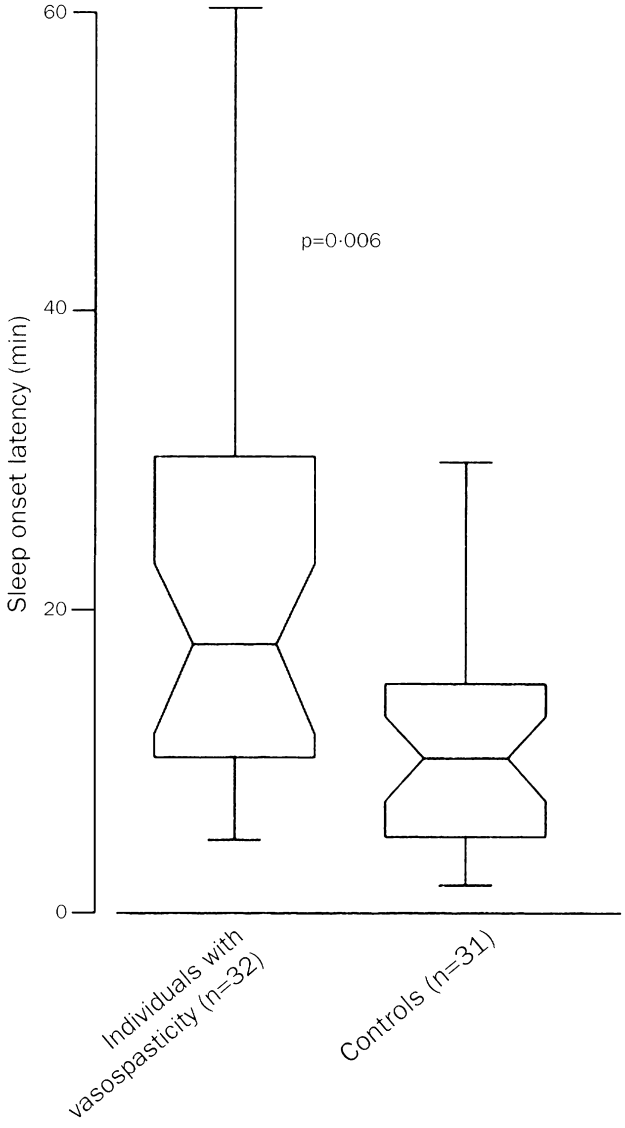

Fig. 4. Sleep-onset latency of night time sleep. Individuals with PVD have prolonged sleep onset time. Boxes = median, 25th, and 75th percentiles; bars = 10th and 90th percentiles. (Reprinted from Pache et al[103] with permission of *Lancet.*)

example, a whiplash trauma, leads to more and longer-lasting symptoms.[128] When exposed to psychological stress, these subjects respond not only with cold hands but sometimes also with color changes in the face.

PVD AND DRUG SENSITIVITY

People with PVD indicate that they tolerate poorly certain systemic drugs and therefore often prefer complementary medicine, based on our own observation. Indeed, the analysis of ABC transport proteins revealed major differences between PVD and non-PVD subjects explaining the differences in drug sensitivity (Fig. 3).[134] When treating these patients with systemic drugs such as beta-blockers or calcium channel blockers, a much lower dose can achieve a full pharmacological effect while minimizing side effects. For other classes of drugs, such as painkillers, they need the same or even higher doses to get sufficient effects.[27]

PVD AND SLEEP BEHAVIOR

Patients with PVD, on average, have a longer sleep-onset time and their sleep is more often interrupted (Fig. 4).[103] The sleep-onset time depends on the body temperature;[20] warm feet are a prerequisite for falling asleep.[82] Patients with PVD, on average, have colder feet and therefore need longer to warm them up, explaining the prolonged sleep-onset time.[83] Correspondingly, warming feet

TABLE 1

Diseases That Lead to Local or Systemic Vascular Dysregulation

Autoimmune diseases	Multiple sclerosis
	Giant cell arteritis
	Lupus erythematosus
	Antiphospholipid syndrome
	Rheumatoid arthritis
	Pre-eclampsia
Infectious diseases	Some bacterial infections (e.g., bacterial meningitis)
	Some viral diseases (e.g. viral liver cirrhosis)
	AIDS
Other possible causes	Cerebral hemorrhage
	Head injury
	Anorexia nervosa
	Mitochondriopathies
	Some tumors (e.g., prostrate cancer)
	Ulcerative colitis and Crohns disease
Drugs (in patients having a predisposition)	Adrenaline
	Alpha II Interferon
	Sumatriptane

up, by taking a bath or wearing socks, decreases sleep-onset time.[20]

SECONDARY VASCULAR DYSREGULATION (SVD SYNDROME)

A number of diseases, especially inflammatory diseases, lead not only to local but also to systemic vascular dysregulation (Table 1). Molecules involved in the inflammatory processes partially enter the circulation and induce more or less systemic effects. A common pathological finding in such diseases is an increased concentration of ET-1 in the circulating blood.[31] ET-1 constricts vessels not only directly but also indirectly by increasing the sensitivity to other vasoconstrictive hormones such as norepinephrine, 5-hydroxytryptamine, and angiotensin-II. Under physiological conditions ET-1 is mainly produced by endothelial cells and the level of ET-1 in the circulating blood is low.[108] However, almost any cell in the body can produce ET-1 when it is under stress; for example, synovial cells in rheumatoid arthritis,[137] or monocytes in HIV[21] or in multiple sclerosis patients.[65] An increase in circulating ET-1 markedly reduces blood flow in the eye[101] and in the kidney,[119] whereas brain circulation is less affected,[76] unless the blood–brain barrier is disturbed. The fact that SVD is due to changes of vasoactive substances in the circulating blood, and the fact that these circulating molecules have a major impact on OBF, especially in the choroid and in the ONH, is the reason why SVD is relevant to ophthalmologists.

SVD AND MULTIPLE SCLEROSIS (MS)

Based on our own observations, patients with multiple sclerosis (MS) often indicate that they had PVD symptoms before they suffered from MS. Once MS is present, however, most of these patients suffer from SVD with increased levels of ET-1,[65] reduced OBF,[101] cold hands, and reduced feeling of thirst.

SVD AND GIANT CELL ARTERITIS

Giant cell arteritis is an immune-mediated vasculitis affecting large- and medium-sized arteries.[1] The affected vessels can occlude, leading to infarction, especially to arteritic anterior ischemic optic neuropathy (AION).[120] In contrast to non arteritic AION, patients with giant cell arteritis suffer often from amaurosis fugax before the acute event and the choroidal perfusion is more affected.[123] In addition, they often respond to calcium channel blockers and they develop slight excavation of ONH.[98] This can all be explained by the fact that besides the occlusion of the inflamed vessels, a temporary but marked SVD with high level of ET-1 induces additional symptoms.[102]

SVD AND SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Systemic lupus erythematodes (SLE) is a condition of chronic inflammation caused by an autoimmune disease. SLE primarily affects women between 20 and 40 years of age and predisposes not only to Raynaud syndrome but even to myocardial infarction in young people.[23] The vascular occlusions in the eye are partially directly due to the inflammation but to some extent also due to systemic SVD with high level of ET-1.[66]

SVD AND CHRONIC RHEUMATOID ARTHRITIS

Patients with chronic arthritis often suffer from reduced circulation of the eye. The synovial cells produce ET-1, leading to an increased level of circulating ET-1.[104,137] An anti-inflammatory treatment, therefore, can indirectly also improve OBF.

SVD AND OTHER AUTOIMMUNE DISEASES

Most of the autoimmune diseases, for example, Crohns disease and colitis ulcerosa, lead to SVD with periods of low blood pressure and reduced OBF.[36,92] Thus, an anti-inflammatory treatment increases blood pressure[78] and improves OBF.

Diagnosis of Vascular Dysregulation

In the clinical setting, the diagnosis of vascular dysregulation relies mainly on the patient history. The history includes cold hands and feet, decreased

feeling of thirst,[131] delayed sleep onset,[83] and low blood pressure.[99] Direct contact of the patient's hands (shaking hands) often yields a sufficient clue for the clinician, in particular if the patient is not aware of having PVD. Thermography is currently used in a research setting to objectify the distribution pattern of the body temperature (Fig. 2).

Clinically unclear cases can be referred to specialized centers for vascular examinations. Nailfold-capillary microscopy, for instance, is of great value in objectifying cold-induced peripheral vascular dysregulation.[37,85,117] The blood flow is measured before, during, and after the cold provocation. The nailfold area is cooled to –15°C. A reduced baseline blood flow velocity, and more characteristically a prolonged flow stop after cold provocation, can be observed in patients with vascular dysregulation.[38] Laser Doppler flowmetry (LDF) of the choroid is useful tool to detect vascular dysregulation in the eye.[52,112] The abnormal response of ocular blood flow is evaluated based on the choroidal vascular reaction to isometric hand grip test.[54] The isometric hand-grip test is a specific, sensitive, reproducible, and non-invasive test of sympathetic function with well-studied reflex pathways.[77] During the isometric hand-grip test, the subfoveal choroidal blood flow is measured by means of the LDF.[40] The choroidal blood flow is usually measured three times—at baseline, and during and few minutes after hand-grip test. A decrease in flow of 10% or more during the hand-grip test is considered abnormal.[54,111] Measurement of plasma ET-1 is helpful to confirm the diagnosis in patients with suspected vascular dysregulation, for example, normal-tension glaucoma patients. However, ET-1 can also be increased in other diseases as discussed above and is not specific for glaucoma. The measurement of plasma ET-1 requires a good laboratory and dependable normal values.[90]

Vascular Dysregulation and Ocular Blood Flow

This review focuses on systemic vascular dysregulation. "Systemic" implies the potential involvement of different organs, including the eye.[54,56] Although primary and secondary vascular dysregulation have many symptoms in common, their influence on eye circulation is distinctively different. As a result of increased level of vasoactive molecules such as ET-1, SVD leads to a more-or-less constant reduction of OBF, particularly in the choroid and ONH.[101] SVD, however, does not essentially interfere with the autoregulation in the retina or in the ONH. Although the origin of SVD is very heterogeneous, its effect on the eye is relatively homogenous. By reducing baseline blood flow, it either leads to no symptoms in the eye or to some visual field reduction and a pale ONH.[27] In acute situations such as giant cell arteritis, it can lead to amaurosis fugax and marked reduction of choroidal circulation.

The effect of PVD on OBF is distinctively different. As the concentration of ET-1 in the circulating blood is only mildly increased, the baseline blood flow is only mildly changed.[7] On the other hand, the regulation of blood flow when challenged is clearly different.[42,53,64] This indicates that OBF is reduced when patients are stressed psychologically or by coldness and OBF regulation can less efficiently compensate for changes in perfusion pressure (disturbed autoregulation).[56] In addition, the response to flickering light is reduced (disturbed neurovascular coupling).[55,114] The velocity of pulse propagation is increased (the vessels are stiffer than in normal eyes),[51,79] and the spatial heterogeneity of the vessel size is increased.[51,79] All this explains why PVD is a major, but SVD only a minor, risk factor for GON. Patients with PVD suffer more often than those with non-PVD from central serous chorioretinopathy, venous occlusion, and arterial occlusion in young age and in glaucoma.[46]

Vascular Dysregulation and Glaucoma

It has been postulated for decades that ischemia might somehow be involved in the pathogenesis of GON.[29] For instance, blood flow velocity is, on average, slower in the retina, in the choroids,[19,46] and in the ONH[47,88,107] in patients with glaucoma, in particular, normal-tension glaucoma. Blood flow is also reduced in retrobulbar vessels[9,35,74,95,107,118,122] and in peripheral capillaries.[22,39,61,97] Classical risk factors for atherosclerosis like smoking, dyslipidemia, diabetes, and systemic hypertension[6,18,89] were astonishingly weakly related to GON. In addition, diseases leading to OBF reduction (e.g., multiple sclerosis), although sometimes leading to atrophy of the ONH, do not lead to a significant excavation of ONH. We therefore postulated some years ago that GON is less linked to a stable reduction of OBF, but rather to an unstable OBF, leading to a repeated mild reperfusion injury.[27,28] OBF is unstable if either perfusion pressure fluctuates markedly (and thereby exceeds the capacity of autoregulation), or if autoregulation, itself, is disturbed.[43,48,97] Indeed, a number of studies found autoregulation altered both in normal-tension glaucoma patients and in POAG patients progressing despite a normalized IOP,[43,121] as the mean ocular perfusion pressure decreased despite the increase in vascular resistivity.[43] The major cause of a disturbed autoregulation is a PVD syndrome.[42] This PVD, in

turn, seems often to be due to a vascular endotheliopathy.[8,12,68]

As mentioned previously, subjects with PVD have low blood pressure. Interestingly, both PVD[16] and systemic hypotension have been identified as risk factors for GON and the progression of GON.[3,6,14,17,44,61,72,75,132] It has been suggested that low blood pressure as well as nocturnal over-dipping increases the probability of visual field deterioration in normal-tension and high-tension glaucoma patients despite good IOP control.[44] Moreover, a prospective long-term study found that progression of visual field defect does not only occur in patients with over-dipping, but also in patients with non-dipping[132]—indicating that a dip deviating from the physiological range is associated with the progression of glaucoma. Such a lack of the physiologic dipping seems to be an independent risk factor for glaucoma progression.[75] The observation that both non-dipping and over-dipping are associated with GON indicates that an underlying vascular dysregulation, and not simply a low perfusion pressure, might be causal. PVD can therefore be considered as a risk factor occurring independently of IOP,[75,100,132] but acting in concert with IOP by rendering the eye more sensitive to IOP. This explanation is supported by the observation that the presence of GON and its progression is in patients with PVD more closely related to IOP than in glaucoma patients without PVD.[61,121] In summary, PVD is characterized by an altered regulation of blood flow including autoregulation. This, in turn, may lead to unstable oxygen supply, which seems to be a relevant component in the pathogenesis of GON.

Method of Literature Search

A systematic search of the Medline database using the PubMed Web site for the years 1966 through June 2007 was conducted using the following key words: *autoregulation, blood flow, blood flow regulation, blood pressure, Endothelin-1, endothelium, drug sensitivity, feeling of thirst, glaucoma, nitric oxide, sleep behaviour, vascular dysregulation, vasospasm.* All articles read were in English and German, and when articles in other languages were of relevance, their abstracts in English were read. The Old Medline was searched for articles published between 1953 and 1965 using the same keywords.

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