invited review

Syncope, cerebral perfusion, and oxygenation

JOHANNES J. VAN LIESHOUT,1,2 WOUTER WIELING,1,2 JOHN M. KAREMAKER,1,3 AND NIELS H. SECHER4,5
1Cardiovascular Research Institute Amsterdam and Departments of 2Medicine and 3Physiology, Academic Medical Center, University of Amsterdam, 1105 AZ Amsterdam, The Netherlands; and 4The Copenhagen Muscle Research Center and 5Department of Anesthesia, Rigshospitalet, University of Copenhagen, DK-2100 Copenhagen, Denmark

Van Lieshout, Johannes J., Wouter Wieling, John M. Karemaker, and Niels H. Secher. Syncope, cerebral perfusion, and oxygenation. J Appl Physiol 94: 833–848, 2003; 10.1152/japplphysiol.00260.2002.—During standing, both the position of the cerebral circulation and the reductions in mean arterial pressure (MAP) and cardiac output challenge cerebral autoregulatory (CA) mechanisms. Syncope is most often associated with the upright position and can be provoked by any condition that jeopardizes cerebral blood flow (CBF) and regional cerebral tissue oxygenation (cO2Hb). Reflex (vasovagal) responses, cardiac arrhythmias, and autonomic failure are common causes. An important defense against a critical reduction in the central blood volume is that of muscle activity (“the muscle pump”), and if it is not applied even normal humans faint. Continuous tracking of CBF by transcranial Doppler-determined cerebral blood velocity (Vmean) and near-infrared spectroscopy-determined cO2Hb contribute to understanding the cerebrovascular adjustments to postural stress; e.g., MAP does not necessarily reflect the cerebrovascular phenomena associated with (pre)syncope. CA may be interpreted as a frequency-dependent phenomenon with attenuated transfer of oscillations in MAP to Vmean at low frequencies. The clinical implication is that CA does not respond to rapid changes in MAP; e.g., there is a transient fall in Vmean on standing up and therefore a feeling of lightheadedness that even healthy humans sometimes experience. In subjects with recurrent vasovagal syncope, dynamic CA seems not different from that of healthy controls even during the last minutes before the syncope. Redistribution of cardiac output may affect cerebral perfusion by increased cerebral vascular resistance, supporting the view that cerebral perfusion depends on arterial inflow pressure provided that there is a sufficient cardiac output.

Address for reprint requests and other correspondence: J. J. van Lieshout, Academic Medical Center, Univ. of Amsterdam, Dept. of Internal Medicine, F4-264, PO Box 22700, 1100 DE Amsterdam, The Netherlands (E-mail: j.j.vanlieshout@amc.uva.nl).

A SYNCOPE OR “COLLAPSE”1 is a sudden loss of consciousness and postural tone. A syncope can be provoked by any condition that jeopardizes cerebral oxygenation. Most commonly a syncope is reflex mediated, also designated “neurally” or “vasovagal,” and it typically develops in the upright position but may even occur in the supine or seated positions, e.g., in the dental chair (14, 154, 176). There is a belief that the human cardiovascular system is exquisitely adapted for maintaining cerebral perfusion in the upright posture. Although the gravitational force creates pressure gradients in the circulation, humans can stand erect because gravitational pressures become partially neutralized by mechanisms that prevent lower extremity fluid accumulation (155). Nevertheless, ~1 million patients are evaluated for syncope annually in the United States, and ~1% of emergency department visits and hospital admissions are for evaluation of a syncope. Thus syn-

http://www.jap.org  8750-7587/03 $5.00 Copyright © 2003 the American Physiological Society
cope has considerable medical, social, and economic impact: it is common, disabling, and possibly associated with a risk of sudden death (78), yet it is difficult to diagnose (37, 159). Conditions like a reduced central blood volume by bleeding or pooling, anxiety, pain, and also a variety of drugs that affect mean arterial pressure (MAP) and cardiac output (CO) render cerebral blood flow (CBF) inadequate for maintaining consciousness (14, 159, 176).

A perspective on syncope is presented with focus on the adjustment of the cerebral circulation to the upright position. The clinical implications of a syncope and potential countermeasures are discussed with emphasis on the critical dependency of the brain on the distribution of CO and regulation of CBF. Common conditions that jeopardize CBF are highlighted with respect to the major physiological events that are elicited with self-induced syncope, the postural reduction in MAP and CO, and the effects of hypocapnia and straining.

SEQUENCE OF CLINICAL EVENTS

Documented records of the hemodynamic and clinical events that precede a syncope in daily life are difficult to obtain. Consequently, under laboratory conditions voluntarily induced syncopal episodes have been applied to document these events by use of two main approaches. Syncope may be almost instantaneously induced by the combination of hyperventilation and straining (33, 64). The circulatory response is different from that commonly observed after a vasovagal faint in which blood pressure does not overshoot after the event (186). In the “fainting lark” (see below), the reflex vasoconstrictor mechanism is functioning as opposed to the vasomotor failure of the vasovagal syncope. A similar overshoot in blood pressure and mean CBF velocity ($V_{\text{mean}}$) is observed also after a Valsalva maneuver (29, 130, 165). During more gradually induced arterial hypotension, the sequence of events can be studied by inducing vasovagal reactions in volunteers and patients with the use of vasodilating agents, standing and passive head-up tilt (HUT), subatmospheric pressure to the lower part of the body (LBNP), bleeding and/or venous occluding tourniquets, threat of instrumentation or venipuncture, and promoting mental stress (45, 136, 176). Also, observations in patients with cardiac syncope and with autonomic failure have contributed to the understanding of the events that are of importance for developing (pre)syncope symptoms.

The fainting lark: voluntary self-induced instantaneous syncope. The fainting lark is a maneuver that combines effects of acute arterial hypotension by gravity and raised intrathoracic pressure with cerebral vasoconstriction in response to hypopcapnia (64, 81). The maneuver induces almost instantaneous syncope in volunteers (95). The fainting lark has been used by children, high school students, and recruits as entertainment and also in the laboratory for research (64, 81, 95). Squatting in a full knee bend is combined with hyperventilation. The subject then suddenly stands up and performs forced expiration against a closed glottis. The maneuver provokes a precipitous and deep fall in arterial pressure, hyperventilation further reduces CBF, and the subject loses consciousness (Fig. 1; Ref. 185).

Lempert and co-workers (94–96) applied the fainting lark in 59 students aged 20–39 yr who volunteered for self-induction of a syncope. A syncope was induced in 42 of 59 subjects. Prodromal symptoms were short lasting (<5 s), which is not surprising given the combined fall in arterial pressure and CBF. The loss of consciousness lasted 5–22 s. Myoclonic jerks lasting 1–16 s were observed in almost all of the 42 syncopal episodes after falling down. During the syncopal attack, the EEG, as in previous studies, showed a progressive slowing in the delta range and initial increase followed by a sudden reduction of brain-wave amplitude. This was in turn followed by a flattening of the trace (“flat” EEG) and then abrupt return of high-voltage slow activity before the normal background activity was restored. Myoclonic jerks occurring while the EEG is slow and “flat” are apparently of subcortical origin and are postulated to originate from abnormal firing of the reticular formation in the lower brain stem (95).

Vasovagal syncope. Prodromal symptoms and signs are usually reported by individuals experiencing a spontaneous vasovagal syncope in daily life. Prodromal

![Fig. 1. Cerebral blood flow velocity during self-induced syncope ("fainting lark"). At standing up, diastolic cerebral artery blood velocity suddenly drops to zero, finger plethysmogram disappears, and the subject instantaneously collapses with abrupt loss of consciousness and rapid restoration of cerebral artery blood velocity in the supine position. $\text{ETCO}_2$, end-tidal carbon dioxide concentration.][From Ref. 185, with permission.]
signs are also observed when a vasovagal syncope is induced under laboratory conditions. The falls in MAP and cerebral perfusion pressure (CPP) are progressive, yet they are usually more gradual in a developing vasovagal syncope than those experienced with the deliberately induced hypotension. However, in one of three individuals with a vasovagal syncope, the collapse is reported to happen instantaneously and thus without warning (43, 159). Prodromal symptoms may start to appear minutes before the actual faint, but a period of only 5 s is not unusual (19). The patient feels uncomfortable in an ill-defined way. This may be manifested by symptoms of epigastric discomfort and vague nausea, sweating, and a desire to sit down or to leave the room. The pathophysiology of at least some of these symptoms is unclear, although there may be a role for pancreatic polypeptide, which is increased in near-fainting subjects (141). A general vagal discharge causing not only bradycardia but also release of pancreatic polypeptide is thought to be involved, inducing reflex relaxation of the stomach (140, 149).

If early warning symptoms of a syncope are ignored, the mild disturbance intensifies and symptoms like lightheadedness, fatigue, blurred and fading vision, palpitations, and tingling of the ears develop (19, 43, 160). The visual prodromal sensations are by a reduction in blood supply to the retina through the ophthalmic arteries. Because the eye, unlike the brain and brain stem, is not protected by the pressure-equalizing effects provided by the cerebrospinal fluid (CSF) and also because the retina is exposed to the intraocular pressure, collapse of retinal perfusion becomes manifest before the loss of consciousness. This relationship is studied by exposure of subjects to high G forces in whole body centrifuges. Sensations begin with diminution of vision, “gray out” (loss of color vision) that may progress to “blackout.” A blackout takes place when the ischemic retina essentially ceases to function (183). Signs of an impending vasovagal faint are facial pallor, sweating, restlessness, yawning, sighing and hyperventilation, and pupillary dilatation (129, 160). The prodromal phase is most often associated with a relatively rapid heart rate (HR). With continuing hypotension, the individual has difficulty in concentrating, becomes unaware of his or her surroundings, and then loses consciousness and falls. Bradycardia occurs just before the actual faint. The final phase of a vasovagal attack is a rapid loss of consciousness with loss of postural tone. During the faint, the clinical picture resembles that of voluntarily induced syncope by the fainting lark. Myoclonic jerks however, appear to be less common in a spontaneous vasovagal syncope than in voluntarily induced syncope using the fainting lark (43). The duration of unconsciousness is usually brief, lasting less than 5 min. Of additional importance in the clinical picture of vasovagal syncope are the postsyncopeal findings, characterized by profound fatigue, a persistence of pallor, nausea, weakness, sweating and oliguria, and a tendency toward recurrence of the reaction if the individual is returned to upright (43, 160).

**Cardiac syncope.** Syncope associated with a heart block or with cardiac arrhythmias is characterized by the suddenness of its onset and the lack of warning symptoms of cerebral hypoxia and autonomic discharge (19). The syncopal episode may develop in both the erect and the supine position. The patient is pulseless, and loss of consciousness ensues within 10 s and more rapidly when the individual is standing than in recumbency (179). Prolonged asystole provokes myoclonic jerks and incontinence of urine. Recovery is rapid with a sudden return of the pulse, flushing of the face, and usually full orientation of the patient. The flush occurs during an overshoot in arterial pressure. After the syncopal episode, the subject can be mobilized almost immediately. During asystole and vasodepression, cerebral hypoperfusion in the carotid sinus syndrome is normally compensated for by cerebral autoregulation (CA; Ref. 93).

**Syncope due to orthostatic hypotension in patients with autonomic failure.** Symptomatic orthostatic hypotension is the main problem in patients with autonomic failure with characteristic features related to the persistent decrease in MAP. Symptoms include lightheadedness and blurring of vision. A neck ache radiating to the occipital region of the skull and to the shoulders (“coat hanger” distribution) often precedes the loss of consciousness (11). The postulated mechanism of this virtually unique symptom of postural hypotension is ischemia in continuously contracting postural muscles. Other symptoms suggesting impaired muscle perfusion are lower back and buttock ache or angina pectoris. Typically, symptoms develop within minutes on standing or walking and resolve on lying down (11). The symptoms can be considered as prodromal and patients with autonomic failure quickly learn to use them as a warning signal so that they lie down to restore cerebral perfusion. If the patient remains upright, consciousness gradually fades and the patient falls slowly to his or her knees. Sudden postural attacks may, however, also occur. Symptoms and signs of autonomic activation like sweating or a vagally induced bradycardia are absent in patients with autonomic failure.

In the following sections the cardio- and cerebrovascular events that usually take place in the transition to the upright position are discussed. First, the methods used to gauge the cerebral circulation in humans are addressed.

**Cerebral Blood Flow and Oxygenation**

In humans, steady-state values of cerebral perfusion are reported as the clearance of gases including N₂O and ¹³⁵Xe, of a tracer such as indocyanine green, or as the arterial-jugular venous O₂ difference under conditions of assumed stable rate of brain metabolism. Transcranial Doppler (TCD)-determined V̇mean of large cerebral arteries has a favorable temporal resolution compared with the more traditional techniques for assessing CBF. Changes in the local cerebral oxygenation are reflected by functional magnetic resonance
and, more dynamically, by dual-wavelength near-infrared light spectroscopy (NIRS; Refs. 9, 18, 80, 91, 92, 109). Each method has its particular drawbacks that need to be addressed (55, 122).

**Methodological issues.** A disadvantage of most methods is that one CBF determination takes ~15 min (114). This renders such methods impractical for assessment of the rapid changes associated with postural cerebrovascular adjustment (18). Two methods that have the potential to provide for a continuous assessment of changes in CBF are the TCD-determined $V_{\text{mean}}$, e.g., of the middle cerebral artery (MCA), and the NIRS-derived changes in regional cO$_2$Hb. A critical issue is to what extent $V_{\text{mean}}$ reflects volume flow. $V_{\text{mean}}$ is calculated from the frequency distribution of the Doppler shifts, and it is assumed to represent flow velocity in the center of the vessel. In the unlikely case that flow is not laminar, $V_{\text{mean}}$ changes out of proportion to flow. Also, changes in $V_{\text{mean}}$ can be equated to flow only if both the angle of insonation and the vessel diameter at the site of investigation remain stable. The large cerebral arteries are conductance rather than resistance vessels, and changes in MAP within the physiological range appear to have negligible effects on the diameter of the insonated artery. More direct observations made during craniotomy reveal that the vessel diameter does not change significantly during variations in MAP of a magnitude that surpasses the changes manifest in response to orthostasis (42). Also, orthostatic stress, as simulated by LBNP, does not alter the diameter of the MCA as assessed with MR imaging (150); and changes in MCA $V_{\text{mean}}$ seem to follow cerebral $^{133}$Xe clearance (9, 23). Thus the constancy of the MCA diameter during postural stress relates changes in $V_{\text{mean}}$ to those in CBF.

NIRS is based on the transparency of tissue to light in the near-infrared region, and the O$_2$ status-depend-ent changes in absorption in cerebral tissue caused by chromophores, i.e., mainly oxy- and deoxyhemoglobin (O$_2$Hb and HHb) (24, 109). With the use of a modified Lambert-Beer law, changes in light absorption at different wavelengths are measured and tissue oxygenation and metabolism beyond that obtained by venous blood sampling. Angulation of the optodes is of relevance with small interoptode distances (171). The depth of the measured tissue volume is a function of the interoptode distance (55, 109). From studies conducted during carotid surgery, the NIRS-determined cerebral oxygenation reflects the tissue oxygenation, provided that superficial tissue oxygenation is eliminated by spatial resolution (3). Caveats of cerebral NIRS include insufficient light shielding, optode displacement, and a sample volume including muscle or the frontal sinus mucous membrane (109). One approach to overcome the uncertainty of each of the methods is to combine TCD and NIRS because they are based on different physical principles, assuming that concordant changes indicate a change in regional CBF (3, 51, 107, 131, 173). A 50% reduction in MCA $V_{\text{mean}}$ and a 10–15% reduction in cO$_2$Hb are associated with syncope (15, 24, 51, 90, 107, 116, 117).

The intravascular route provides the most accurate method to measure arterial pressure. It is, however, important to appreciate that, e.g., the radial artery may constrict with a ~6% reduction in diameter when under prolonged orthostatic stress and then dilates with appearance of (pre)syncope symptoms (70). In the few patients in whom intracranial arterial pressures have been studied, the percentage of the original pulse pressure remaining in small cortical arteries was on average ~3% less than that remaining in the cervical carotid artery on occlusion of the common carotid artery (5). Thus also intra-arterial pressure may not fully reflect the pressure driving CBF in the large cerebral arteries. Noninvasive measurement of blood pressure as afforded by the Finapres device or other arterial volume clamping systems (2) may bear the same limitation and, in addition, vasoconstriction may affect the intra-arterial to finger pressure transfer. Also, the determination of the critical closing pressure (CrCP) as the pressure-axis intercept of instantaneous finger pressure-velocity relationships may be flawed by a ~70- to 100-ms time lag between the two waveforms, i.e., the additional time required for the pressure wave to reach the finger compared with the time it takes for it to reach the MCA. Dawson et al. (29), however, concluded that this parameter is not critical; without lag compensation, linear regression still produced values for CrCP significantly larger than zero. On a similar vein, arterial CO$_2$ is often inferred by either the end-tidal or the transcutaneous routes, which differ in their temporal resolution, and especially transcutane-
ous measurements of CO₂ may be sluggish. Also, the latency and time constant of the MCA \( V_{mean} \) response to changes in arterial CO₂ are to be taken into account (132).

Noninvasive or minimally invasive continuous tracking of changes in stroke volume (SV) and CO by biomimpedance, ultrasound, and arterial pulse-wave analysis has the potential to appreciate the importance of systemic blood flow for perfusion of the brain. As an example, modeling flow from arterial pressure by simulating a nonlinear three-element model of the aortic input impedance (180) has been applied to study changes in cerebral velocity and/or oxygenation and their relationship to changes in systemic hemodynamics (31, 51, 67, 69, 130, 131, 173). A possible shortcoming shared by all noninvasive methods is that if absolute values are needed, calibration against a method like phase-controlled quadruple thermodilution, Fick, or inert gas-rebreathing is necessary (72, 133, 173). After calibration, the tracking of changes in SV with Modelflow vs. a thermodilution-based estimate changes compared with within 5 ± 2% (mean ± SD) during prolonged HUT (53). If absolute values are not required, the method gives reliable trend data, and changes in CO can be tracked from an arterial pressure waveform that can be as peripheral as the radial artery (75, 180) or finger (53, 172). A general shortcoming is that validation of beat-to-beat tracking of SV is based on conventional measurements of SV like thermodilution-based estimates that are obtained as averages over at least some 20 heart beats (48, 73, 73) and do not reflect the beat-to-beat fluctuations, which may be considerable (166).

**CARDIOVASCULAR DYNAMICS IN ORTHOSTASIS**

*Central cardiovascular variables.* On passive or active assumption of the upright position, the first circulatory event is a gravitational displacement of blood away from the thorax to dependent regions of the body with a fall in venous return (155). Depending on the type of orthostatic stress (i.e., active standing, LBNP, or HUT), 0.5 to 1 liter of blood is transferred to the regions below the diaphragm. Orthostatic pooling of venous blood begins immediately, and the total transfer is almost complete within 3–5 min depending on the investigated body region. In addition to this transfer of thoracic blood, the central blood volume is affected by transcapillary filtration of fluid into the interstitial spaces in the dependent parts of the body in response to the high capillary pressure with little interstitial counterpressure. Continued filtration into the tissue further reduces the circulating volume, although fluid is gained from the tissue above the venous hydrostatic indifference point (128), which is defined as the axial reference within the column of venous blood where pressure is not altered by postural reorientation (128). The pooled blood is not stationary, but in regions of the lower part of the body its transit time is prolonged (138). During 5 min of quiet standing, the hydrostatic load may induce a loss of ~400 ml of plasma water (103). The transcapillary loss of fluid approaches stability after ~20–30 min with a net fall in plasma volume of ~15%, but a steady state is not reached (108). As a consequence of blood pooling and the superimposed decline in plasma volume, the return of venous blood to the heart is reduced and central venous pressure (CVP) falls (173). The end-diastolic filling of the right ventricle is affected, which, in turn, leads to a reduction in SV and a ~20% fall in CO (53). Despite the fall in CO, MAP is preserved by compensatory vasoconstriction of resistance and capacitance vessels in the splanchnic, musculo-cutaneous, and renal vascular beds (138).

The circulatory adjustment to active standing up includes an initial ~30-s lasting fluctuation in MAP followed in 1–2 min by a phase of relative stability. Initially, MAP drops some 25 mmHg as total peripheral resistance falls ~40% for 6–8 s unrelated to orthostasis or straining. This transient fall in MAP is likely to explain the feelings of lightheadedness that even healthy humans sometimes experience shortly after standing up and may even cause recurrent syncope (Fig. 2; Refs. 157, 184). The rapid short-term adjustments to orthostatic stress are mediated exclusively by neural pathways of the autonomic nervous system. During prolonged orthostatic stress, additional adjust-

---

**Fig. 2. Cerebrovascular and hemodynamic response to standing (average of 10 subjects).** Cardiovascular and cerebral perfusion and oxygenation responses to standing in healthy adults. Note the initial fall in middle cerebral artery mean flow velocity (\( V_{mean} \)) and near-infrared spectroscopy (NIRS)-determined cerebral oxygenation at standing up and the reduction after 5 min upright. MAP\(_{mean} \), mean arterial pressure at brain level; \( \Delta O_2 Hb \), cerebral oxygenation; CO, cardiac output; TPR, total peripheral vascular resistance. [From Ref. 51, with permission.]
ments are mediated by the humoral limb of the neuroendocrine system (i.e., renin-angiotensin-aldosterone system). The main sensory receptors involved in orthostatic neural reflex adjustments are the arterial mechanoreceptors (baroreceptors) located in the aortic arch and carotid sinuses. The most important defense against a critical reduction in central blood volume is that of muscle activity, and in everyday life extensive pooling is limited by activation of the skeletal muscle pump (108, 155, 162). Also in the upright moving position, maintenance of sufficient venous return is assisted by the circulatory effects of contracting muscles (7). If the muscle pump is not activated, it results in the syncope that even healthy humans experience (Fig. 3; Refs. 108, 160).

Cerebral perfusion. The $O_2$ supply to the brain depends on the arterial $O_2$ content and the CBF of 50–60 ml·100 g$^{-1}$·min$^{-1}$. The cerebral $O_2$ uptake is $\sim$3 ml·100 g$^{-1}$·min$^{-1}$, accounting for 15–20% of the basal metabolic rate (138). In healthy subjects, an acute lowering of CBF is associated with mild symptoms of cerebral hypoperfusion. Mental confusion becomes prominent with 50–60% reduction, and cerebral oxygenation becomes affected (107, 117).

Standing up places the brain in a most disadvantageous position. In the upright position, the cerebral arteries are positioned some 30 cm above the heart, whereas $\sim$70% of the total blood volume shifts below that level (138). For the brain, not only its in...
the theoretical CrCP (29, 30). During standing up, the rapid drop in CPP takes place too fast to be counter-regulated. This makes the initial drop in CBF proportional to the driving pressure and explains the early fall in cerebral artery Vmean at ~7 s after standing up (Fig. 2). Data on local and sympathetic control of cerebral vessel diameter are unified in the "dual-control hypothesis." This hypothesis states that the pial arterial circulation comprises two resistances in series with extraparenchymal vessels under autonomic neural control and intraparenchymal vessels as the major cerebral vascular resistance bed governed primarily by metabolic and myogenic factors (113, 170).

Taken together, the cerebral circulation is considered to consist of the large cerebral arteries that passively follow changes in transmural pressure, the pial arterial circulation including two segments subject to different CA mechanisms (113, 170), and the venous cerebrovascular bed behaving as a Starling resistor (4, 41, 85, 167, 170).

REGULATION OF CEREBRAL BLOOD FLOW

The relative constancy of the overall craniospinal volume ("the Monro-Kellie doctrine"; Refs. 79, 169), the cerebrovascular anatomy, and the variations in CPP related to the ever-changing position of the cerebral circulation relative to the heart make the intracranial hemodynamics during orthostasis extremely complex (110, 169). Control of cerebral perfusion is linked closely to regulation of the intracranial volume. Control of flow compromises the arterial cerebrovascular bed, the large cerebral veins, and the processes associated with production and reabsorption of CSF (44, 169). According to Poiseuille’s law, CBF is determined by the CPP and the cerebrovascular conductance, or its reciprocal, cerebrovascular resistance (CVR) (1). The CPP is the difference between MAP at the level of the circle of Willis and ICP, and ICP, in turn, encompasses CPP is the difference between MAP at the level of the bed, the large cerebral veins, and the processes associated with production and reabsorption of CSF (44, 169). According to Poiseuille’s law, CBF is determined by the CPP and the cerebrovascular conductance, or its reciprocal, cerebrovascular resistance (CVR) (1). The CPP is the difference between MAP at the level of the circle of Willis and ICP, and ICP, in turn, encompasses CPP and the CSF pressure. The variable resistance to flow is encountered in the cerebral arteriolar bed mainly; the major cerebral conductance arteries are in principle noncompliant and act merely as a conduit for the pulsatile arterial flow from the aorta to the brain (120). CBF is dynamically adjusted to changes in the perfusion pressure, the metabolic activity of the brain, humoral factors, and autonomic nerve activity (18).

A characteristic feature of the cerebral circulation is that CBF tends to remain relatively constant over a range of systemic blood pressures, termed CA. The actual range of pressures may vary between subjects (91, 92). CA secures CBF by modulation of vascular smooth muscle responses, effectively buffering changes in ICP at the background of the limited intracranial compliance (126). In the following sections, the local and systemic regulatory mechanisms that participate in CA are highlighted, and the behavior of CA during orthostasis and syncope is discussed.

Cerebral autoregulation: local control. The proposed mechanisms operating at the level of cerebral vascular smooth muscle tone include myogenic, metabolic, neural, and endothelial factors (126). The myogenic hypothesis suggests that cerebral vascular smooth muscles constrict or relax in response to, respectively, an increase or a decrease in the transmural pressure (the "Bayliss effect"; Refs. 6, 38, 39). Both Kontos et al. (86) and MacKenzie et al. (105) studied the responses of cerebral precapillary vessels to changes in MAP in the cat. Vessel responses were found to be size dependent and capable to adjust flow over most of the pressure range (41, 170). Changes in transmural pressure produce vasoconstriction by affecting the membrane electrical properties of MCA muscle (50). Nitric oxide influences basal cerebral vascular tone under normal conditions and mediates vascular responses to diverse stimuli including hypoxia-induced cerebral vasodilatation (35, 177). The metabolic hypothesis holds that CBF is controlled by metabolites with vasoactive properties, including CO2, H+, potassium, adenosine, and calcitonin-gene-related peptide. Yet, although these substances have vasodilatory properties, for each of these metabolites studies with contradictory results have been reported (for review, see Ref. 126).

Cerebral autoregulation: autonomic effects. The sympathetic innervation to the cerebral vasculature is largely via the superior cervical ganglion (113). Stimulation or denervation of these nerves affects resting CBF only marginally (113, 126), but inconsistent effects on CBF as reported in animals may be attributed to both species differences and effects of anesthesia (18, 57, 71). Inactivation of neural traffic by neurotoxin does not affect the flow-pressure relationship in the cat cerebral vessels, and until recently the sympathetic nervous system was held to exert an only insignificant tonic influence on cerebral vessels under physiological conditions (18). Yet there are data that do not conform to that. First, in humans MCA Vmean decreases during unilateral trigeminal ganglion stimulation (178). Vice versa, as estimated with single-photon-emission computed tomography, CBF increases after stellate ganglionic blockade (168). Second, studies both in healthy subjects and in patients with cardiac insufficiency support the view that cerebral perfusion may be affected by sympathetically mediated cerebral vasoconstriction as a consequence of a reduction in CO. During dynamic exercise, MCA Vmean and CO2Hb increase (58, 68, 76). However, this increase is attenuated or absent in patients with cardiac insufficiency (59) and in patients with atrial fibrillation (67). When during cycling the ability to increase CO is limited by cardioselective β1-adrenergic blockade in healthy subjects, the increase in MCA Vmean is reduced (69). Taken together, these observations suggest that a reduced ability to increase CO induces peripheral vasoconstriction not only in working skeletal muscle (127) but also in the brain. Sympathetic blockade at the level of the neck blunts this pharmacologically induced limitation in the rise in Vmean (66), supporting an influence of sympathetic nerves on CBF in humans (143). Equally, in patients with severe heart failure, CBF is reduced substantially but increases after cardiac transplantation (47). Thus, in response to a decline in CO, an
increased sympathetic drive may also contribute to cerebral vasoconstriction. As an example, in the standing position the decrease in blood pressure at the level of the brain is well within the CA range but the reduction in CO is substantial (~20%).

The postural decrease in cerebral artery $V_{\text{mean}}$ and in $cO_2Hb$ is not fully accounted for by the associated reduction in the arterial CO2 tension ($P_{CO_2}$; Refs. 98, 190), and the finding that steady-state CBF or MCA $V_{\text{mean}}$ as $cO_2Hb$ decrease on standing (Fig. 2) seems to be at odds with the traditional concept of CA, i.e., that CBF is relatively constant within a wide range of perfusion pressure (12, 51, 98, 99, 107, 112, 126, 130, 144, 147, 173, 190). Also diurnal changes in CO relate to MCA $V_{\text{mean}}$ (31). In general, cerebral perfusion is independent of CO, for as long as MAP remains normal or almost normal. The mentioned observations support that cerebral perfusion depends on arterial inflow pressure but also suggest that CO is important. This is not unexpected when considering that the brain represents only 2% of the body mass but that it receives ~15% of CO (138). A limitation to all studies that relate changes in CBF, MAP, and CO is that it has not been possible to measure MAP at the MCA or other large intracranial vessels and $V_{\text{mean}}$ is taken as “a surrogate” for CBF. Thus, when relating changes in measured variables that are supposed to reflect CBF, MAP, and CO, we may remain uncertain on what happens to the true cerebral perfusion pressure and blood flow.

$CO_2$. CO2 is a potent vasodilator of cerebral vessels, and CBF increases with an increase in $P_{CO_2}$ (97) independent of CA (1, 18, 54, 80, 92, 115, 132). Conversely, hypocapnia induces constriction of the smaller cerebral arteries. Effects of CO2 on the myogenic response of CA depend on several factors, e.g., $H^+$ concentration, perfusion pressure, and endothelial function (89, 115). In humans, the CO2 chemoreflexes and arterial baroreflexes are intertwined at a variety of levels (60, 121). The caliber changes of the resistance vessels in response to CO2 (the “CO2 reactivity of the brain”) interfere with CA (100, 169, 170). The limits of MAP within which CA operates are modified by sympathetic activity and by $P_{CO_2}$ (126); i.e., CA becomes less effective as $P_{CO_2}$ increases (54, 152). In subjects with orthostatic intolerance, hypocapnia may contribute to a reduction in MCA $V_{\text{mean}}$ and $cO_2Hb$ (51, 109, 118), whereas an increase in inspiratory CO2 raises MCA $V_{\text{mean}}$ and may improve orthostatic tolerance (10, 118).

Apart from its cerebrovascular effects, CO2 exerts an influence on the systemic circulation that could provoke a syncope. Hypocapnia reduces arterial vascular resistance, resulting in a small reduction in MAP (16, 64, 121, 135). When autonomic cardiovascular reflexes are malfunctions or absent, the systemic vasodilatory effects of hypocapnia become more obvious (121).

Static and dynamic components of autoregulation. CA needs to have both fast- and slow-acting regulatory components to span the range of prevailing demands on CBF in everyday life (1, 164). Dynamic CA refers to an ability to restore CBF in the face of MAP changes within seconds and reflects the latency of the cerebral vasoregulatory system (123). Static CA reflects the overall efficiency of the system. Accordingly, the classic CA curve represents the static behavior of the CA as quantified by time-domain-based analysis (123). The consequence of a latency of the CA mechanism is that brisk and short-lasting changes in pressure will be transmitted more or less unmodified to flow.

Methods proposed to assess the dynamic CA are based on analysis of oscillations in cerebral artery $V_{\text{mean}}$, most often in the MCA, either spontaneous or induced by short reductions or increments in MAP, in the time or frequency domain (24, 122, 164, 165). Frequency-domain methods classify CA according to the coherence, transfer function, and phase-frequency response between $V_{\text{mean}}$ and MAP as assessed by spectral and cross-spectral analysis. Transfer gain increases substantially with frequencies from 0.07 to 0.20 Hz in association with a gradual decrease in phase (189). The many data thus obtained indicate that attenuation of oscillations in $V_{\text{mean}}$ in response to changes in arterial pressure may be more effective at low than at high frequencies and allow CA to be interpreted as a frequency-dependent phenomenon (34, 125, 189). As yet it is uncertain whether the various methodologies that claim to quantify the static and dynamic components of CA are interchangeable (122, 164).

In healthy subjects, variations in MCA $V_{\text{mean}}$ precede variations in MAP at the spontaneously occurring oscillation in MAP at 0.1 Hz (34, 116, 189) and with a coherence that declines with frequency (125, 189). The phase-lead of MCA $V_{\text{mean}}$ in advance of MAP and the frequency-related reduction in coherence are interpreted as the result of CA operating in this frequency range with the quality of a high-pass filter (34, 123, 189). At high frequencies, less cerebral attenuation of MAP oscillations to MCA $V_{\text{mean}}$ implies that the CA cannot respond fast enough to rapid changes in MAP (123). The transient fall in MCA $V_{\text{mean}}$ on standing up is an example of the slowness of CA adjustment (Fig. 2). Interestingly, the initial decline in MAP on standing is comparable for the young and the elderly, but the reduction in $V_{\text{mean}}$ in older subjects is small, which was interpreted as indicative for enhanced CA in the elderly (99).

The lower limit of cerebral autoregulation. Lassen (91) reported that, below a certain limit, cerebral vessel diameter, CBF, and MAP change proportionally. In most studies, determination of CA is based on quantification of the complex relationship of CBF and MAP, the latter taken to represent CPP. CA is evaluated by pharmacological and physical manipulation of MAP, the latter often by deliberate pooling of blood by LBNP or by postural stress. Olsen et al. (119) determined the lower limit of CA (LLCA; Ref. 41) by reducing MAP to 50% of control by using labetolol infusion and LBNP. For the maintenance of sufficient cerebral perfusion in upright humans, the LLCA is of special interest. The LLCA is identified in a variety of anesthetized animals by bleeding (105) and in humans subjected to pharmacologically and/or posture-induced hypotension (90).
The values found in both animals and humans vary, again attributable to species differences, use of anesthetic agents in many animal experiments, and the methodology used to elicit hypotension and to gauge the produced changes in CBF (41, 122). Patients with orthostatic hypotension related to sympathetic failure tolerate a reduction in MAP remarkably well, suggesting that the LLCA is not a fixed value and that it may shift toward a lower MAP (51, 163).

There is room for methodological concern in the evaluation of the LLCA in that the approaches used for its determination by decreasing MAP through bleeding, postural stress, and/or vasodilatation inevitably produce a concomitant reduction in CO. It should be considered that under these conditions, the effects of MAP and CO on CBF cannot be examined separately. As an example, when CO is rigorously controlled as is the case during cardiopulmonary bypass surgery, CBF is independent from CPP for a range of pressures (36, 114).

STRAINING AND G FORCE: IMPACT ON CEREBRAL PERFUSION

In the standing position, straining is highly effective in inducing a syncope. Power lifting may occasionally lead to dizziness and even to fainting, suggesting that especially in the upright position CBF is compromised. Syncope is reported for weight lifting when the intrathoracic pressure increases to −160 mmHg (25). The concomitant elevation in CVP during intensive exercise may protect cerebral perfusion by counteracting the rise in MAP (131), although MCA \( V_{\text{mean}} \) decreases during heavy resistance training (32). The weight lifters’ blackout (25), like self-induced syncope (64, 96), may be attributed to a critical reduction in CBF due to preexercise hyperventilation (33). Equally, a syncope is observed occasionally during playing of wind instruments (13). Intense expiratory strain with a nonphysiological elevation of CVP is likely to cause a critical reduction in CPP.

In supine humans, intracranial tissue pressure approximates CVP, and an elevation in CVP by straining would induce a parallel increase in the cerebral outflow pressure. During straining in the supine position, there is indeed a close relation between MCA \( V_{\text{mean}} \) and the MAP-to-CVP difference as an indication of CPP (130). This is, however, not so during standing, and by standing the small influence of a 40-mmHg elevation in CVP for cerebral outflow pressure could reflect a collapse of outflow resistance veins (4). During straining, the changes in MCA \( V_{\text{mean}} \) are of a greater magnitude than those established in MAP. This may indicate either a delay in activation of the CA or the inability of CA to cope with the magnitude and speed of the changes in MAP. Dawson et al. (29) proposed that the large drop in CrCP at the end of straining reduces CVR and explains the large increase in MCA \( V_{\text{mean}} \). Also during prolonged coughing, intrathoracic and abdominal pressures are transmitted via the great veins to the intracranial compartment (49), causing a transiently elevated pressure with a critical impairment of CBF and syncope (111, 153).

**G force.** During exposure to \( +G_z \), loss of consciousness occurs in aircrew flying high-performance aircraft. This phenomenon is responsible for several aircraft losses with accompanying loss of life since 1938 (17). In a recent survey among jet pilots flying fighter aircrafts with rapid-onset rates, a minority reported \( G \)-induced loss of consciousness, although almost all had experienced \( +G_z \)-related grayouts and/or blackouts to the high sustained \( +G_z \) forces (188), and an in-flight reduction of \( \text{CO}_2\text{Hb} \) during aerial gunnery training missions has been demonstrated (83).

ORTHOSTATIC INTOLERANCE AND COUNTERMEASURES

Postural stress by relaxed standing or passive HUT may reduce orthostatic tolerance in healthy subjects who otherwise never faint. In both young and elderly subjects with no history of fainting, addition of invasive instrumentation during prolonged HUT increases the incidence of a vasovagal syncope (74). It should also be considered that vasovagal responses are not necessarily abnormal; the as-yet-unidentified neural pathways involved in the response are probably present in all healthy humans with individual differences in susceptibility (175). The medical history in suspected vasovagal syncope is essential, and tilt-table testing is mainly useful to confirm the diagnostic suspicion.

The functional derangement in vasovagal syncope is a withdrawal of muscle sympathetic nerve activity with strong evidence for an early loss of vasomotor tone in the majority of fainting subjects (175). In healthy volunteers subjected to prolonged HUT, Madsen et al. (106) demonstrated that cerebral perfusion is maintained by peripheral vasoconstriction in muscle and skin until the onset of vasovagal syncope when muscle perfusion becomes increased at the expense of blood flow to the brain. Many of the premonitory symptoms of a vasovagal syncope are indicative for cerebral hypoperfusion (118). However, with respect to the index used to infer CVR, controversies exist regarding interpretation of TCD before and during a syncope (20, 147). The pulsatility index [PI; \( \text{systolic velocity} - \text{diastolic velocity}/\text{mean velocity} \)] is proposed as a parameter of downstream cerebrovascular resistance but has not been evaluated for this purpose. PI does not take into account the prevailing level of blood pressure, and Czosnyka et al. (26) restrained its value as an index of CVR for as long as BP and HR are relatively stable. At syncope, while MAP falls, diastolic and mean cerebral and carotid blood flow velocities diminish, whereas the fall in systolic velocity is limited (Fig. 4; Ref. 84). During a vasovagal syncope, PI vs. CVR, expressed as the ratio of MAP to MCA \( V_{\text{mean}} \), may provide conflicting results with a decrease in CVR but a rise in PI (20, 77, 147). Some have considered the increase in PI to reflect defective CA (46), whereas others have interpreted the reduction in CVR to indicate that CA is intact at the appearance of a syncope (147). The reduc-
tion in diastolic flow velocity during a syncope (Fig. 1), even becoming zero, may be interpreted as a collapse of downstream vessels when the diastolic blood pressure decreases below the CrCP of the cerebral vessels (20, 77, 147). Also calculation of CVR as the ratio of the pressure drop to flow across the vascular bed is complicated by the difficulty in directly determining the pressure drop because the values of ICP and CBRVP are unknown (65). With orthostatic stress, the assumption of a constant intracranial or venous pressure may be flawed and, if so, in the upright position MAP/MCA Vmean does not provide the same information about CVR as when supine (65, 182). Alternative methods to interpret changes in CVR such as an estimate of CrCP or the inverse of the CrCP-regression slope, the resistance-area product, are proposed (20, 123). Accounting for CrCP in the estimation of CVR may provide a more physiological explanation for the temporal relationship between MAP and MCA Vmean during rapid changes in MAP (20, 21, 29, 65, 142, 181).

Differences in the postural circulatory adaptation between subjects who faint vs. those who do not are subtle and do not permit to predict the occurrence of fainting (161). Subjects with orthostatic intolerance or postural tachycardia syndrome, however, present with a disproportionately greater effect of postural stress on HR and CO than on MAP. This has been attributed to an abnormal functional distribution of central sympathetic tone to the heart and vasculature (40, 158). Some individuals who are orthostatically intolerant maintain a normal MAP, and, in the absence of systemic hypotension, a reduction in MCA Vmean may even result in syncope (Fig. 4; Refs. 46, 52, 102, 151). In these patients, a symptomatic reduction in MCA Vmean during standing is a consistent finding and may reflect the adjustment to a critically limited CO (46, 52, 102, 118, 147).

During maximal hyperventilation, MCA Vmean may fall ~55% (82, 118). Controversy exists as to whether the decrease in MCA Vmean results from excessive sympathetic outflow to the cerebral vasculature (146) or from hyperventilation-induced hypocapnia (88) that...
may affect CrCP and CVR (1, 27, 124). A link between the postural decline in MCA \( V_{\text{mean}} \) and \( CO_2 \) was demonstrated by Cencetti et al. (22), but the contribution of the decrease in \( CO_2 \) to the reduction in MCA \( V_{\text{mean}} \) is as yet undefined. The finding that at \(-30 \) mmHg LBNP \( CO_2 \) does not change but \( V_{\text{mean}} \) becomes reduced suggests that \( CO_2 \) does not fully account for the postural reduction in MCA \( V_{\text{mean}} \) (190). \( CO_2 \) levels and indexes of cerebrovascular resistance decrease during presyncope, and CrCP may increase to levels approaching MCA diastolic blood pressure before decreasing precipitously on syncope (20).

Similarly, the interpretation of the data on dynamic CA in presyncope subjects, as gauged in the time and frequency domain, is under dispute (123, 148, 190). Data from temporal sequence analysis suggest that during fainting changes in \( V_{\text{mean}} \) precede the fall in MAP (28), but this may equally be explained by the concomitant effects of a presyncopal decline in \( CO_2 \). In healthy subjects during LBNP, the reduction in steady-state \( V_{\text{mean}} \), together with the increase in transfer function gain of MAP to \( V_{\text{mean}} \) is interpreted to indicate a deterioration of CA and a possible contribution to the development of a (presyncope) (190). However, in subjects with recurrent vasovagal syncope provoked by HUT, dynamic CA does not differ from that of controls (20, 148). Considering that a postural reduction in MCA \( V_{\text{mean}} \) as in \( CO_2Hb \) in humans is the rule, these findings may be interpreted as being the result of the intrinsic adaptive responses of a functioning dynamic CA to a sometimes critical postural reduction in CO rather than to a malfunctioning of CA per se (52).

Countermeasures. Several approaches have been advocated to alleviate symptoms in patients with orthostatic intolerance, including drug treatment, volume expansion, physical countermaneuvers, and endurance training. Subjects with orthostatic intolerance should be warned to avoid immobility and encouraged to increase their leg muscle mass because even moderate training improves orthostatic tolerance in deconditioned subjects (145). Exercise also promotes retention of fluid in the upright posture (104). When considering that pooling of blood is the major cause in the development of orthostatic intolerance, maneuvers that counteract this transfer of blood are beneficial. Raising muscle tension of the legs attenuates the decrease in MAP generated by LBNP (156). In patients with sympathetic failure, leg muscle tensing increases MAP and reduces symptoms of orthostatic intolerance (174). In healthy subjects with normal orthostatic tolerance, leg tensing does not affect MAP but elevates CVP and CO and attenuates the postural reduction in MCA \( V_{\text{mean}} \) as in \( CO_2Hb \) (162, 173). Leg tensing can also abort an imminent faint (Fig. 5; Ref. 87).

CONCLUSIONS

During standing, cerebral autoregulation is challenged by the position of the cerebral circulation through the reduction in arterial inflow pressure, cerebral perfusion pressure, and cardiac output. A syncope is mostly associated with the upright position. Vasovagal responses, cardiac arrhythmias, and autonomic failure are the common causes. The most important defense against a critical reduction in the central blood volume is that of the muscle pump and, if it is not used, even normal humans faint shortly after standing. Continuous tracking of CBF velocity by TCD and NIRS-determined cerebral tissue oxygenation have contributed to the understanding of the cerebrovascular adjustments to postural stress in health and disease; e.g., MAP does not necessarily reflect the cerebrovascular phenomena associated with a (pre)syncope. Studies on dynamic CA in presyncope that take into account both MAP and \( V_{\text{mean}} \) indicate a decrease in cerebrovascular resistance with a complex interplay between vasoconstriction and vasodilatation preceding a syncope. The dynamic component of CA is assessed by methods that are based on analysis of oscillations in MCA \( V_{\text{mean}} \) related to MAP in the time or frequency domain. CA may be interpreted as a frequency-dependent phenomenon, with less cerebral attenuation of MAP oscillations to MCA \( V_{\text{mean}} \) at high frequencies. The clinical implication is that the CA cannot respond fast enough to rapid changes in MAP, as seen in the transient fall in MCA \( V_{\text{mean}} \) on standing up. It is as yet uncertain to what extent in the earlier stages of (pre)syncope with MAP still within CA limits, the (pre)syncopal reduction in cerebral perfusion and oxygenation results from excessive sympathetic outflow to the cerebral vasculature or from hyperventilation-induced hypocapnia. When a syncope progresses, it is the fall in MAP below the lower limit of CA that reduces cerebral perfusion and oxygenation further to unconsciousness. In subjects with recurrent vasovagal syncope, dynamic CA seems not different from that of healthy controls. Redistribution of CO may affect cerebral perfusion by increased cerebral vascular resistance, supporting the view that cerebral perfusion depends on arterial inflow pressure given a sufficient CO.

This work was supported by grants from the Netherlands Heart Foundation (NR. 99-182) and the Danish National Research Foundation (504-14).

REFERENCES


J Appl Physiol • VOL 94 • MARCH 2003 • www.jap.org


