Controversial Issues Concerning Norepinephrine and Intensive Care Following Severe Traumatic Brain Injury

John F. Stover, Peter Steiger, Reto Stocker[1]

Abstract

Norepinephrine and corresponding intra- and interorgan pathways are of clinical pathophysiologic and pharmacologic importance as exaggerated activation needs to be reduced and insufficient activation must be supported to prevent further deterioration and therapy-induced organ damage. This is of high relevance in critically ill patients in whom various norepinephrine-influenced organ systems are simultaneousy affected with varying degrees of tolerability and resistance to norepinephrine-induced cell damage and finds its maximal challenge in patients suffering from severe traumatic brain injury (TBI). This comprehensive review describes complex pathophysiologic interactions, including hemodynamic, microcirculatory, hormonal, metabolic, inflammatory, and thrombocytic alterations overshadowed by differential consequences of commonly applied pharmacological interventions following TBI. Overall, investigations published to date suggest that receptor-dependent effects of norepinephrine might predispose to complex evolving deterioration especially during intensive care which is characterized by differentiated complication-driven changes and specific complication-dependent needs. In this context, thrombocytes and leukocytes with their adrenergic receptors and differential norepinephric functional regulation are ideal candidates to influence all organs at once. Despite its secure integration of norepinephrine in clinical routine, future emphasis must be directed at unmasking, monitoring, and controlling possible receptor-mediated detrimental influences which could offset anticipated organ protection.

Key Words

Catecholamines · Secondary injury · Monitoring · Critical care

Eur J Trauma 2006;32:10–27

DOI 10.1007/s00068-006-0004-4

Introduction

An integral part of modern therapy aimed at preventing secondary injury following traumatic brain injury (TBI) is to maintain adequate cerebral perfusion. Elevating mean arterial blood pressure(MABP) and cerebral perfusion pressure (CPP) is achieved pharmacologically by continuously infusing vasopressors, e.g., norepinephrine. Experimental conditions following TBI mainly focus on early cerebral changes during short continuous norepinephrine infusion which does not necessarily reflect critically ill pati-ents. As outlined in the schematic drawing (Figure 1) challenge to improve our understanding and thus ameliorate modern treatment modalities following TBI is to simultaneously consider the temporal profile of local and evolving systemic alterations with potential reciprocal influences which are simultaneously influenced by current therapeutic interventions. Although catecholamines are readily used in critically ill patients, differential organ-specific changes induced by catecholamines need to be considered and should be monitored to prevent affecting the anticipated neuroprotection. This comprehensive review focuses on pathophysio-logically relevant inter- and intraorgan norepinephric pathways and characterizes various potentially harmful pharmaco-

[1]Department of Surgery, Division of Surgical Intensive Care Medicine, University Hospital Zürich, Zürich, Switzerland.

Received: January 12, 2006; accepted: January 19, 2006

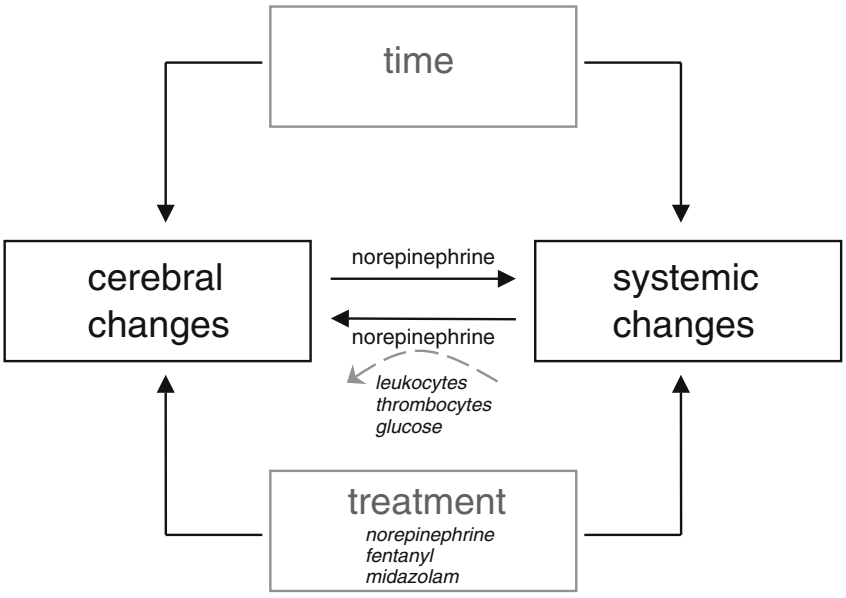


Figure 1. Schematic drawing depicting the principal pillars of simultaneous time-dependent pathophysiologic and pharmacologic changes which balance beneficial and disadvantageous norepinephrine-mediated actions. In critically ill patients, specific needs are dictated by characteristic changes over time, possibly requiring individual adjustment of interventions, making detailed monitoring indispensable.

dynamic effects of continuous norepinephrine infusion within the routine intensive care treatment of patients suffering from severe TBI.

Endogenous Release and Exogenous Norepinephrine Administration

Within minutes following a stressful event, activation of the hypothalamic–pituitary–adrenal axis amplifies release of norepinephrine, epinephrine, and cortisol from the adrenal gland [1]. These exhaustive alterations maintain hemodynamic stability, mobilize energetic reserves, influence the immune system, and adapt neuroendocrinological and hormonal alterations [1, 2]. Activation of the noradrenergic locus coeruleus stimulates various neuronal functional networks responsible for the increased level of alertness and sustained analgesia, and inhibits secretion of various hypothalamic and pituitary hormones, thereby suppressing reproductive, growth and thyroid functions [2]. The magnitude of this response reflects the extent of underlying injury and contributes to subsequent worsening if not controlled [3]. Under clinical conditions, norepinephrine is infused continuously together with volume resuscitation and hemorrhage/coagulation control to maintain defined blood pressure or CPP levels (Figure 2). In parallel, the sustained endogenous sympatho-autonomic activity is reduced by sedatives and analgetics.

Organ-Specific Effects of Norepinephrine

Extensive investigations of acute and chronic norepinephrine infusion have revealed important influences on various organs which, among others, depend on administered dose, organ-specific receptor distribution, and binding availability of these receptors. Overall,

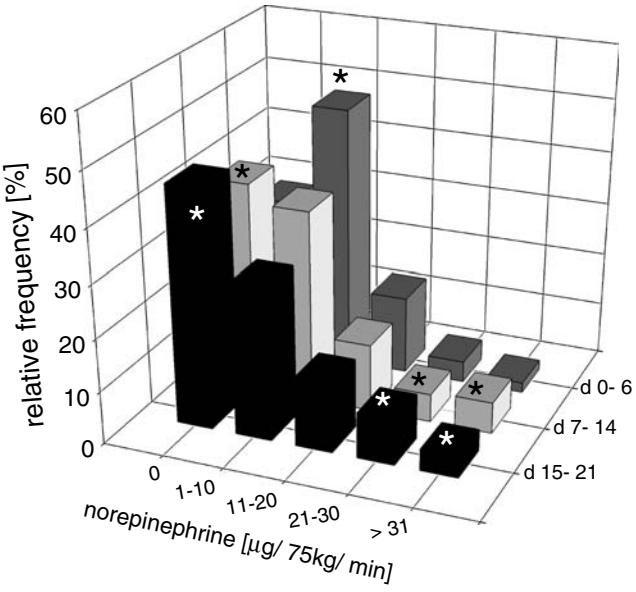


Figure 2. Relative frequency distribution of norepinephrine dose in 50 patients suffering from severe TBI up to 3 weeks following injury. Norepinephrine dose was adjusted to maintain CPP between 70 and 110 mmHg. During the first week predominant norepinephrine dose ranged from 1–10 µg/min. While the majority of patients stabilized, reflected by the sustained frequency without norepinephrine and the decreasing frequency within the norepinephrine dose ranging from 0.013–0.133 µg/kg/min, patients with a more difficult clinical course showed an increased frequency in high norepinephrine dose exceeding 21 µg/min (≅0.28 µg/kg/min) (*p<0.001).

beneficial effects on individual organs may be offset by simultaneous alterations of other organ systems which demand following a '*brain-oriented*' and avoiding a '*brain-centered*' therapy. In this context, norepinephrine-driven improvement of cerebral perfusion and metabolism due to increased CPP occurs in face of reduced kidney, liver, and testis perfusion and metabolism [4]. The general concept of modern intensive care treatment is to guarantee adequate volume replacement and catecholamine administration within acceptable, i.e., organ-protecting limits. While increased volume administration allows to significantly reduce norepinephrine dosage [5], prevention of organ-endangering volume overload must be considered. Careful judgement of the individual situation is required to guide sequential or parallel administration of norepinephrine and fluids. In principal, single administration of high-dose norepinephrine in a patient in whom intravascular volume is depleted or reduced should be avoided as norepinephrine-mediated vasoconstriction will induce organ damage. A careful review of the literature produced only few clinical studies investigating the pharmacodynamic and pharmacokinetic profile of continuous norepinephrine infusion in healthy volunteers, nonseptic, and TBI patients. The majority of findings are derived from hemodynamically instable patients suffering from sepsis and corresponding experimental sepsis models in various species. Given the facts that sepsis fulfills the same criteria of the systemic inflammatory response syndrome (SIRS) expanded by a bacterial infection and that SIRS can even develop in patients with isolated severe TBI [6], certain changes observed during these conditions might also be of relevance for the treatment of TBI patients, especially if sepsis develops. The complexity and diversity of posttraumatic intensive care involving various norepinephrine-influenced organs is depicted in the schematic drawing (Figure 3).

Heart, Circulation, and Macrohemodynamics

According to its characteristic receptor distribution, norepinephrine increases cardiac contractility (β_1) and peripheral resistance (α_1 receptors), thereby elevating systolic and diastolic blood pressure, increasing MABP, cardiac index, and total peripheral resistance (TPR) [7–11]. Pressure-dependently, coronary perfusion is improved in healthy animals [7]. However, norepinephrine might endanger cardiac viability as chronic administration of high-dose norepinephrine induces left ventricular hypertrophy [12–14] and may activate cardiotoxic cascades via stimulation of β_1-adrenergic-driven apoptotic changes due to intracellular activation of Ca^{2+}-activated calmodulin kinase and release of free oxygen radicals which is inhibited by β_2 stimulation [15]. It is important to keep in mind that improving MABP does not necessarily reflect ameliorated organ perfusion especially under pathological conditions [8, 10]. Despite normalized MABP, failure of improving impaired renal and mesenteric perfusion [8, 10] could reflect maintained autoregulation or insufficient increase in MABP due to massively disturbed autoregulation. This is also suggested by recent findings in septic patients in whom a further increase in MABP from 65 to 85 mmHg did not improve renal function [16].

Lungs

Apart from pressure- and volume-passive influences, norepinephrine interferes with pulmonary function by activating adrenergic receptors and stimulating the inflammatory response. Under experimental conditions, norepinephrine dose-dependently induces α_{1A}- and α_{1B}-adrenergic-mediated pulmonary vasoconstriction [17] which can be inhibited by fentanyl in vitro [18]. High-dose norepinephrine (0.1 mg/kg/h ≅ 1.7 µg/kg/min, 128 µg/75 kg/ min) continuously infused up to 72 h in healthy rats results in reversible pleural effusion and pulmonary venous congestion related to increased hydrostatic pressure [13]. The reversible left ventricular hypertrophy appears necessary to compensate and clear pleural effusion upon termination of norepinephrine infusion [13]. In addition, adrenergic-mediated inflammatory response with alveolar and interstitial edema formation contributes to functional and structural lung injury [14]. Under pathological conditions, the lungs are primed for sustained accumulation, activation, and sequestration of leukocytes [19] which could be aggravated by infused norepinephrine. Vasoconstriction in combination with increased leakage could impair preexisting regional perfusion/ventilation mismatch in intubated and ventilated ICU patients.

Intestines

α-adrenergic and β-adrenergic activation influences gut motility and intestinal functions. Splanchnic vasoconstriction shunts blood to heart, lungs, brain, and muscles. While epinephrine reduces intestinal and splanchnic perfusion leading to mucosa damage [20, 21], norepinephrine at 0.05 µg/kg/min (≅3.75 µg/75 kg/min) is not associated with negative effects in animals and patients [8, 9, 22] as it does not impair intestinal perfusion and mucosal integrity despite a dose-dependent increase in splanchnic oxygen extraction [9]. Even under adverse conditions, as e.g. sepsis with or without ensuing shock high-dose norepinephrine at 0.18 or 0.45 µg/kg/min is not harmful [20, 21]. Norepinephrine is superior to

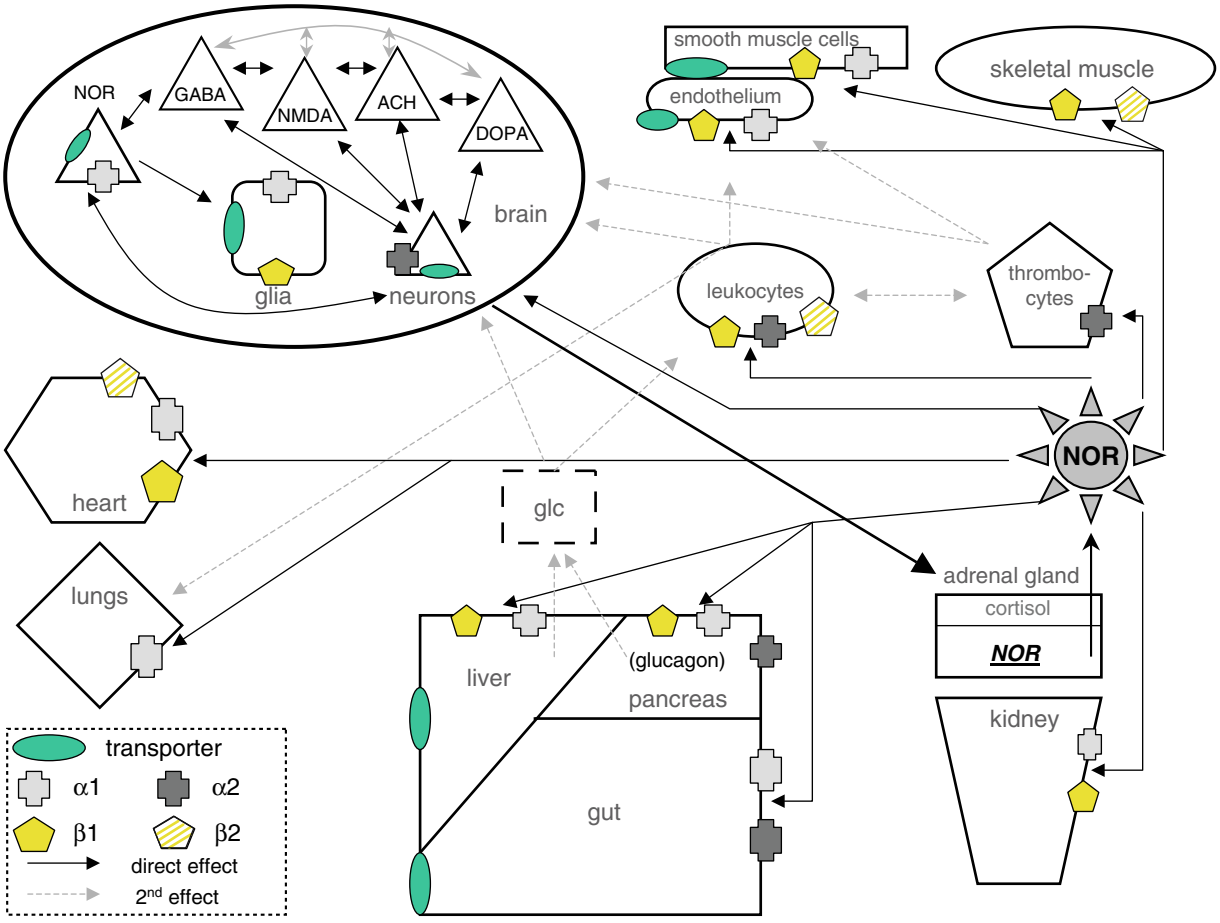


Figure 3. Schematic drawing of different organ systems with their complex intra- and interorgan influences involved in norepinephrine-mediated functional circuits. An unspecific stressful event stimulates adrenal release of norepinephrine which then receptor-dependently stimulates, inhibits, or disinhibits subsequent pathways with their own secondary cascades (specific details are given in the main text). Intravenously infused norepinephrine targets the same adrenergic receptors. The intact lines depict direct or primary norepinephrine-mediated effects; the broken lines show secondary effects involving leukocytes, thrombocytes, and elevated glucose levels, possibly inducing or aggravating cell damage (details are described in the main text).

phenylephrine, dopamine, vasopressin, and epinephrine by improving splanchnic perfusion, oxygen delivery, and lactate uptake [23–26].

Kidneys

The strong oxygen dependency and low critical threshold for oxygen consumption in combination with the required high renal perfusion pressure (kidney: 80–180 mmHg vs. liver: 50–150 mmHg) make the kidneys highly vulnerable to impaired perfusion and oxygen supply [27, 28]. Apart from volume administration, norepinephrine is beneficial, especially in face of nitric oxide (NO)-mediated vasodilation and disease-related vasoparalysis which disturbs various modulators (catecholamines, NO, angiotensin II, vasopressin, and endothelin-1) and intracellular pathways [29]. Despite norepinephrine-induced reduction in renal perfusion observed in healthy volunteers at 0.118 ± 0.03 µg/kg/min [30], norepinephrine pressure-dependently elevates renal perfusion, increases urine output and creatinine clearance in healthy [7, 31] and septic animals [31]. Adverse effects were ruled out in a retrospective study including 200 cardiac surgery patients in whom norepinephrine infusion did not increase serum creatinine levels [32]. Under experimental and clinical septic conditions norepinephrine required to elevate MABP to 70 mmHg needs to be increased severalfold [31, 11], reaching values as high as 1.3 ± 0.3 µg/kg/min (≅97.5 ± 22.5 µg/75 kg/min) in humans [11] or 3.1 ± 0.3 versus 0.2–1 µg/kg/min (≅232.5 ± 22.5 µg/75 kg/min vs. 15–75 µg/75 kg/min) in septic versus control rats [8]. While increasing MABP in nonseptic patients does not alter renal

function [11, 32], suggesting intact autoregulation, elevating MABP from 51 ± 3 to 79 ± 7 mmHg in septic patients significantly increases urine flow and creatinine clearance [11]. This, however, is contrasted by the recently published findings that an increase in MABP from 65 to 85 mmHg does not improve renal function in septic patients [16]. Filtration and resorption processes are under adrenergic influence: renal vasoconstriction in conjunction with stimulated β_1 secretion of renin with subsequent activation of the vasoconstrictor angiotensin II and release of aldosterone results in decreased glomerular filtration and increased retention of sodium, reducing loss of fluid via urine. In addition, norepinephrine decreases tubular sodium secretion.

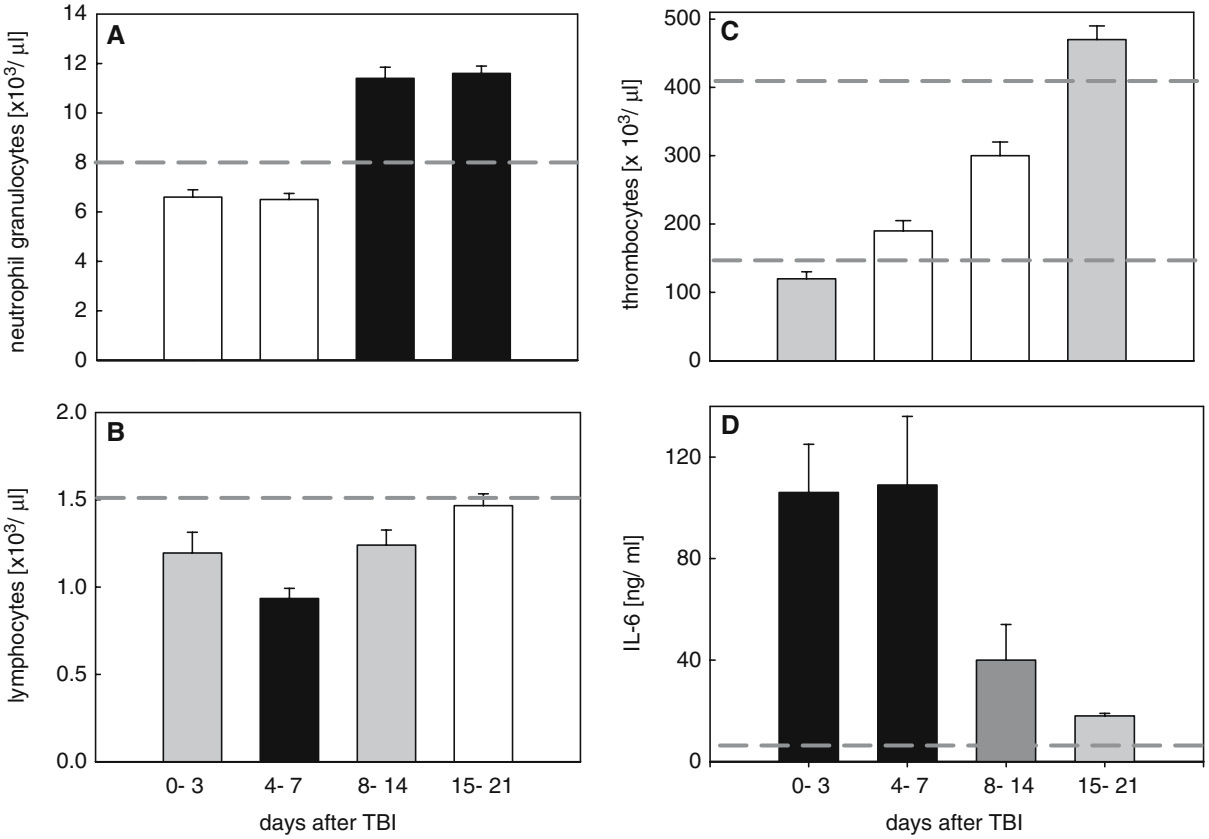
Metabolism

Complex Regulation of Lipolysis, Proteolysis, Glycolysis, and Glycogenolysis

Catecholamines differentially influence actions of insulin and glucagon, hormones which control fat, protein, and glucose metabolism. In critically ill patients, sustained release of proinflammatory and catabolism-aggravating cytokines [33] occurs in face of disturbed hormonal regulation, impaired nutrient uptake, and sustained metabolism. Lipolysis mediated by activation of α_2 and β_1-adrenergic receptors and regulated at the level of cAMP production by different intracellular cascades releases free fatty acids and glycerol and produces free oxygen radicals [34, 35]. Proteolysis is not only restricted to injured muscle due to activation of the ubiquitin/proteasome system, calcium- and calpain-dependent release of myofilaments from the sarcomere and upregulation of macrophage-associated lysosomal proteolysis [36, 37], but involves all muscles as observed clinically by the generalized muscle loss in critically ill patients without any obvious muscle trauma. Thus, norepinephrine by itself or in conjunction with glucocorticoids, cytokines, and altered insulin responsiveness with inadequate amino acid supply can induce myofibrillary breakdown and insufficient synthesis [38, 39]. Sustained ATP and oxygen consumption of β-adrenergic-stimulated muscular Na^+–K^+–ATPase could contribute to muscle degradation. Norepinephrine-induced proteolysis [40] has been challenged by recent reports suggesting anabolic effects via stimulation of β_2- and β_3-adrenergic receptors in rats [41]. For the complex regulation of glucose metabolism, activation of α_2-adrenergic receptors inhibits insulin secretion, thus elevating blood glucose levels due to attenuated uptake in myocytes and lipocytes while stimulation of α_1- and β-adrenergic receptors increases pancreatic release of insulin which decreases blood glucose due to increased cellular uptake and intracellular degradation [42]. During critical care with disturbed peripheral glucose uptake and metabolism [43], the predominant α_1-adrenergic stimulation with sustained hepatic gluconeogenesis and glycogenolysis will increase blood glucose levels during high-dose norepinephrine infusion [21, 44]. In addition, pancreatic glucagon release stimulated by α_1, α_2, and β receptors increases blood glucose [45, 46]. In healthy volunteers, norepinephrine at 0.1 µg/kg/min significantly increases glucose production and uptake [47]. In patients, norepinephrine at 0.18 or 0.45 µg/kg/min [21] elevates blood glucose ≥10 mM (180 mg/dl) which aggravates underlying brain damage and impairs survival [48] due to local acidosis and sustained cerebral inflammatory response. Thus, increased insulin administration might become inevitable whenever high-dose norepinephrine is required to maintain certain MABP and CPP levels.

Oxidative Metabolism and Organ Energetics

As observed in healthy volunteers, norepinephrine dose-dependently increases whole body oxygen consumption between 0.06 and 0.2 µg/kg/min which could contribute to adverse effects in critically ill patients [49] despite increasing oxygen delivery, especially with underlying disturbed cell function. Under clinical conditions, the use of more invasive procedures, including pulmonary artery catheter, transjugular cannulation of the hepatic vein, assessment of hepatic indocyanine-green clearance, endoluminal positioning of a tonometric gastric tube and laser Doppler catheters allows to determine cardiac index, hepatosplanchnic oxygen extraction, lactate production, alanine uptake, and blood flow, gastric mucosal pCO_2 production, and jejunal mucosal perfusion, respectively [9, 21]. In septic patients, norepinephrine significantly increases splanchnic oxygen and lactate extraction. Elevated lactate predominantly results from β-adrenergic-stimulated muscular Na^+-K^+-ATPase which is then oxidized by hepatic gluconeogenesis (Cori cycle). These effects are mainly mediated by epinephrine [50] or high-dose norepinephrine. The dose-dependent increase in splanchnic oxygen extraction especially in patients with low baseline cardiac index values < 2.4 l/min/m^2 suggests that intravascular volume depletion had not been restored [9]. Under experimental conditions, parameters of organ energetics as e.g., ATP, phosphocreatinine, and lactate/pyruvate ratio determined in the muscle, liver, gut, kidney, and heart, as well as humoral arterial parameters (glucose, lactate, lactate/pyruvate ratio, ketone body ratio) are not altered by norepinephrine at 0.2 µg/kg/min in otherwise healthy rats [8].



Figures 4a to 4d. Temporal profile of changes in neutrophils (a), lymphocytes (b) thrombocytes (c) and IL-6 (d) determined in 20 patients with severe TBI up to 3 weeks following injury. The dashed lines reflect upper (neutrophils, IL-6) or lower normal limits (lymphocytes, thrombocytes). Color-coded bars reflect the degree of pathological deviation from normal values (black: strong; dark grey: moderate; light grey: mild; white: normal).

Inflammatory response

Complex Alterations Contributing to Cellular Dysfunction

The inflammatory response comprises a plethora of complex cellular and humoral alterations which support local inflammation aimed at confining existing tissue damage by concomitantly inhibiting systemic inflammation to prevent uncontrollable damage of other primarily uninjured organs. However, this fine-tuning is disturbed in critically ill patients, resulting in SIRS [6]. TBI induces local and systemic inflammation as evidenced by an upregulation of intestinal NF-κB, ICAM-1, TNF-α, and IL-6 [51, 52].

Differential Influence of Norepinephrine

Initially, β_2-adrenergic activation increases circulating lymphocytes derived from the marginal pool and the spleen, while α-adrenergic activation subsequently elevates circulating neutrophil granulocytes released from the marginal pool and the lungs [53] due to reduced adhesion to vascular endothelium [54]. Subsequently, lymphopenia with a mismatch between T helper and T cytotoxic lymphocytes with sustained neutrophil activity [55] develops. Released proinflammatory cytokines, in turn, can influence central noradrenergic pathways [56]. Overall, norepinephrine interferes with immunocompetence [57] which could contribute to evolving multiorgan failure [58] (Figures 4a, 4b, and 4d). Norepinephrine induces apoptosis, impairs mitochondrial membrane potential in lymphocytes and natural killer (NK) cells [59], inhibits cytokine secretion, target binding, and programming for cytotoxicity in NK cells [60] and suppresses phagocytosis, generation of oxygen radicals, and neutrophilic and lymphocytic chemotaxis during prolonged adrenergic stimulation [61, 63]. In addition, norepinephrine dose-dependently inhibits oxygen consumption in nonstimulated human peripheral blood mononuclear cells, while in activated cells β-adrenergic receptors are desensitized and α-adrenergic receptors are sensitized, resulting in sustained norepinephrine-mediated stimulation of oxygen consumption [62]. Dendritic cells important in fine-tuning

the appropriate immune response to invading pathogens and tolerance to self-antigens are under differential β-adrenergic control [64]. In addition, β-adrenergic activation controls release of pro- and antiinflammatory cytokines [44, 65, 66] and contributes to depressed cell-mediated inflammation by stimulating the peroxisome proliferator-activated receptor gamma (PPARgamma), a nuclear hormone receptor that mediates antiinflammatory actions [67], as well as inhibiting NF-κB and activating I-κBα [68, 69]. At low norepinephrine concentrations (≈20 nM), α_2 receptor activation stimulates TNF-α and IL-1β production in hepatic Kupffer cells which is inhibited by high concentrations via β_2-adrenergic receptors [56]. β_2-adrenergic stimulation also induces cellular immunosuppression by downregulating various receptors on stimulated human peripheral blood mononuclear cells [70]. A loss in endogenous norepinephrine appears crucial in inducing, maintaining, and impairing resolution of brain inflammation [71].

Thrombocytes

Physiological Control of Organ Function

Thrombocytes are crucial in functionally interlocking coagulation with the innate immune system [72]. Apart from stopping hemorrhage by receptor-mediated (P-Selectin) adherence to endothelial cells, leukocytes, and other thrombocytes [73], thrombocytes activate the coagulation cascade and release a multitude of different mediators which also control vascular tone, e.g., serotonin, norepinephrine, thrombin, prostacyclin, histamine, and bradykinin. Thrombocytes restrict local tissue injury, recruit and activate neutrophils through the release of IL-8 [61], enable leukocyte tissue penetration and further thrombocyte aggregation via release of matrix-degrading metalloproteinases [74]. The functional complexity is reflected by the plethora of intracellular pathways [75], and the involvement of cytokines (TNF-α) and endothelial cells (NO) within the regulation of thrombus formation [76].

Pathological Response

Exaggerated local thrombocyte–leukocyte activation can impair microvascular blood flow [77, 78] and compromise thrombocyte-mediated stabilization of endothelial cells and protection against oxidative tissue injury [79] as increased neutrophil activation and induced endothelial damage result in a burst of free radicals and release of digestive enzymes also observed in thrombocytopenic patients suffering from multiorgan disease [80]. P-Selectin-activated pathways promoting leukocyte and thrombocyte adhesion contribute to post-traumatic brain edema formation in knock-out mice [81]. Released thrombin exerts neurotoxic effects, impairs memory functions, and decreases cerebral perfusion under experimental conditions [82] which is inhibited pharmacologically [83]. Following severe injury, elective orthopedic surgery or vascular graft insertion, thrombocytes are in a state of increased activation as judged by expression of surface proteins, release of soluble adhesion molecules [84–89], hyperaggregation, and sustained adhesiveness [90–92].

Noradrenergic Influence

Formation of thrombocyte–neutrophil aggregates as well as receptor expression on thrombocytes and neutrophils are increased through α-adrenergic stimulation [93], possibly aggravating disease-related changes. α_2-adrenergic stimulation activates intracellular cascades and dose-dependently promotes thrombocyte activation [94, 95] which is inhibited pharmacologically [94, 96, 97]. Sustained norepinephrine-stimulated activation with subsequent consumption and peripheral sequestration of thrombocyte-bound leukocytes can decrease circulating thrombocytes and contribute to multiorgan failure [85, 98, 99] (Figure 4c).

Brain

Transmitter and Local Functional Circuits

The excitatory neurotransmitter norepinephrine originates in the locus coeruleus and lateral tegmental nuclei of the brain stem from where it activates different diencephalic and telencephalic regions, modulates cortical neuronal acitivity, induces arousal and alertness, enables memory formation, consolidation, reinforcement, and information retrieval [100–109] by influencing hippocampal input [110]. Norepinephrine also modulates hormone release from pineal gland [111], pituitary [112–114], and hypothalamus [115], influences processing of arterial chemoreceptor afferent inputs [116], coordinates respiratory pacemaker and nonpacemaker neurons [117], and controls the esophageal–gastric relaxation reflex [118] by α-adrenergic receptors. Age-related reduction in cortical noradrenergic neurotransmission affects spatial learning and memory performance [119]. Norepinephrine exerts anti- and prooxidative functions on various isolated neurons [120–122]. As all transmitters, norepinephrine not only influences neuronal and glial function but is also subject to site-dependent regulatory influences by other transmitters: norepinephrine stimulates glial release of ATP which regulates postsynaptic efficacy of glutamatergic neurons [123]; activation of presynaptic cholinergic receptors facilitates noradrenergic transmission [124]; stimulation of presynaptic $GABA_A$ receptors on glutamatergic

neurons within the locus coeruleus contributes to the excitability and activity of noradrenergic neurons due to functional disinhibition [125]; noradrenergic stimulation of basal ganglia and cortical glutamatergic neurons can be inhibitory (α_2) [126, 127] or excitatory (β_1) [126]; activation of α_1 receptors inhibits dopamine release in midbrain neurons [128] but induces dopamine release in the medial prefrontal cortex [129]; hippo-campal and cortical norepinephrine release are under glutamatergic and dopaminergic influence [129, 130]; α_2-adrenergic presynaptic activation diminishes norepinephrine release and reduces the inhibitory action of GABA-ergic inputs in brainstem neurons, thereby disinhibiting histaminergic neurons [131]; glial glutamate uptake is mediated by α_1-adrenergic stimulation and inhibited by β-adrenergic activation [132].

Vasoregulation

Apart from static, myogenic, and metabolic influences, including various circulating and local endothelial mediators, norepinephrine modulates proximal, large diameter segments of cerebral arteries and arterioles (10–20 µm). The resulting local vasodilation and vasoconstriction assures constancy of cerebral perfusion with MABP values ranging from 50–170 mmHg. Endogenous norepinephrine released from adrenergic neurons in close apposition to vessels and glia [133] stimulates Ca^{2+}-mediated astrocytic-driven vasoconstriction [134], and activates β_2 receptors on nitrigeric nerve terminals, thereby releasing vasodilating NO while co-localized α_2 receptors inhibit NO release and mediate vasoconstriction [135]. Exogenous norepinephrine primarily targets endothelial α- and β-adrenergic receptors as the BBB with its enzymes [136] and specific transporter localization inhibits free norepinephrine penetration [137]. However, α-adrenergic-induced endothelial permeability enables uncontrolled passage with subsequent neuronal and glial activation [138].

Metabolism

In addition to its effect on glial glycogenolysis and glycolysis [139], glycogen synthesis [140, 141], and glutamine uptake [142], norepinephrine increases lactate uptake in cultured mouse cortical neurons [143] to assure sufficient energy transfer from astrocytes to neurons under conditions of increased energetic demand.

Glucose-Dependent Changes

Hypoglycemia activates central counter-regulatory processes to correct low blood-glucose levels and avoid brain damage. In this context, glutamatergic stimulation of the sympathoadrenal and hypothalamic-pituitary adrenal axis [144], and release of norepinephrine within the ventromedial hypothalamus result in central α_2- and β-adrenergic activation [145] and adrenal secretion of counter-regulatory hormones [146].

Plasticity and regeneration

Within the functional and structural complexity of the brain, various transmitters including norepinephrine receptor-dependently modulate excitability and modify neuronal threshold for activity-dependent synaptic changes which influence cortical plasticity [147], prolong survival of cultured human neuroblastoma cells, induce neuronal differentiation, and influence synaptic connectivity [148]. Further evidence supporting norepinephrine-mediated regeneration is found in the facts that noradrenergic depletion increases cerebral inflammation [149] and that administration of clonidine, which selectively reduces α_2-mediated synaptic norepinephrine release and reduces plasma catecholamine levels [150], impairs posttraumatic functional recovery and even reinstates neurological deficits [151, 103].

Norepinephrine and Traumatic Brain Injury

Following TBI, norepinephrine is of clinical interest for several reasons: (1) disturbed cerebral noradrenergic circuits contribute to evolving brain damage; (2) these changes give rise to potential pharmacological targets ameliorating neuropsychological and cognitive disturbances; and (3) infused norepinephrine is used to improve reduced cerebral perfusion following TBI.

Posttraumatic Changes in Brain Norepinephrine and Potential for Pharmacologic Regeneration

Cerebral Functional and Structural Disturbances

Following an initial transient increase, norepinephrine turnover is depressed in TBI rats [152, 153] which together with reduced axonal transport and decreased brain norepinephrine amount induces behavioral and psychological abnormalities [154]. Furthermore, disturbed noradrenergic circuits upregulate potentially harmful excitatory pathways [152] and constrict isolated rat middle cerebral artery [155] and posttraumatic pial arterioles [156], inducing injury-aggravating cerebral ischemia.

Differential Pharmacological Targets

The initial sustained clearance of norepinephrine from the extracellular space is thought to be autoprotective and should not be influenced pharmacologically as this promotes edema formation [153]. The subsequently depressed norepinephrine turnover, however, should be targeted to support noradrenergic influence on regen-

eration, plasticity, behavioral, and cognitive improvement [157–159]. In this context, α_1 and β_1-adrenergic antagonists (prazosin; propranolol) and α_2-adrenergic agonists (clonidine) should not be given, as these drugs impair cognitive functions [160] and reinstate neurological deficits [151, 161] without worsening or inducing histological damage. This is in sharp contrast to the differential pharmacologic interventions used within the LUND concept, an ICP-oriented, low CPP-controlled and volume-guided treatment paradigm, where clonidine and metoprolol together with low-dose thiopental and continuous fentanyl and midazolam infusion are used [162]. Posttraumatic disturbance of the noradrenergic system shares certain similarities with pathophysiological alterations involved in depression and Parkinson's disease. Thus, norepinephrine, mixed serotonin/norepinephrine, and dopamine/norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, amphetamines (norepinephrine release and inhibited uptake), amantadine and memantine (NMDA receptor antagonists with dopamine release), L-DOPA (norepinephrine precursor), and bromocriptine (dopamine agonist) used to treat these chonic neurodegenerative diseases have been in focus to ameliorate posttraumatic psychomnestic deficits [163]. First clinical trials with small patient numbers showed promising results in treating posttraumatic depression and improving cognitive functions following administration of milnacipran, desipramine, or amantadine [164–166]. Based on experimental data in non-TBI rats, additional α_2-adrenergic inhibition to increase extracellular norepinephrine [167] as well as repetitive administration are required to induce beneficial effects, since antidepressants usually need 2–3 weeks of chronic administration before cellular and clinical alterations are detected [168, 169]. Unfortunately, psychostimulative antidepressants carry side effects [163] and may also impair memory consolidation [170]. Modulating α-adrenergic changes may be age-or model-dependent [171] which makes a simple transfer from bench-to-bed difficult. Prospective controlled studies are required to evaluate the beneficial effects of adjuvant neuropsychopharmacotherapy started early after TBI, i.e., before patients are transferred to neurorehabilitation centers.

Posttraumatic Changes in Cerebral Perfusion and Metabolism

Secondary Damage

In principal, severe TBI is characterized by a primary lesion which can be worsened during its clinical course owing to secondary injuries [172] – e.g., insufficient cerebral perfusion which is considered a treatable and avoidable event.

Regional and Temporal Heterogeneity

Observational studies reveal regional and temporal heterogenous changes in perfusion (hypoperfusion, vasospasm, and hyperemia) [173], metabolism (hypo- and hypermetabolism [174] with enzymatic disturbances [175]), and vascular reactivity [176]. Norepinephrine can influence these alterations. This regional and temporal heterogeneity conveys to pharmacologically targeted perfusion deficits, which, in turn, requires intensified monitoring to avoid exaggerated and insufficient treatment. In this context, experimentally elevating MABP and CPP at 24 h after TBI, when pericontusional perfusion normalizes, induces hyperemia [177]. Hyperemia, a sign of impaired cerebral autoregulation [178], elevates ICP and could aggravate brain damage via norepinephrine-induced increase in hydrostatic pressure or receptor-mediated activation of detrimental cellular changes.

Norepinephrine-Induced Increase in MABP, Cerebral Perfusion and Metabolism

Apart from the endogenous increase in metabolism-driven cerebral perfusion [179], norepinephrine dose-dependently increases MABP which – depending on the investigated species and the induced level of arterial hypertension [155] – increases cerebral blood flow (CBF) and metabolism [180, 181], has no effect [182], increases CBF without influencing glucose metabolism [155] or even decreases CBF [183, 184]. With a structurally injured or functionally impaired BBB encountered following TBI [185] and induced by norepinephrine [184], respectively, infused norepinephrine can penetrate the brain [186] and increase CBF via β-adrenergic activation of glial and neuronal activity [181, 183]. Norepinephrine-induced increase in cerebral perfusion also improves cerebral oxygenation in rats [177, 187] and patients [188–190]. The pressure-dependent increase in cerebral perfusion is also related to widening of spastic cortical arterioles and flushing of vessels with microthrombosis as revealed by in vivo intravital microscopy in TBI rats [177]. Contrary to experimental conditions, the norepinephrine-ameliorated cerebral perfusion and reduction in ischemic brain volume in patients was not associated with increased cerebral metabolism, possibly related to the concomitant administration of sedatives and analgetics. In fact, cerebral oxygen consumption was significantly reduced, possibly related to increased inflow of sedatives and analgetics or reversal of ischemic changes due to improved perfusion [191]. As observed under experimental conditions, norepinephrine-induced regional alterations might contribute toprolonged increase in CBF [187], related to locally released vasoactive mediators – e.g., NO and augmented

cellular activity. Sustained NO production due to increased glutamate-mediated neuronal activity induces cGMP-dependent smooth muscle relaxation resulting in vasodilation and increased perfusion to meet metabolic demands. In addition, catecholamines could contribute to vasodilation by scavenging free radicals [119] which have been shown to inactivate NO [192]. The significant increase in extracellular pericontusional glutamate concentrations related to β-mediated reduced glial glutamate uptake [131], sustained neuronal release, and facilitated penetration via a damaged BBB could explain the increased cortical EEG activity [187]. Alternatively, elevated EEG power could reflect preserved neuronal integrity due to improved tissue perfusion and oxygenation.

Increased Posttraumatic Brain Damage

To avoid additional posttraumatic ischemic damage, MABP and the calculated CPP are increased and maintained ≥70 mmHg which prevents an increase in cortical contusion volume in TBI rats [193]. However, experimental and clinical studies clearly show that CPP values ≥ 90 mmHg are indispensable to increase and normalize local cerebral perfusion [177, 187, 191]. Consequently, higher norepinephrine amounts are required. This, in turn, could increase the risk for additional norepinephrine-dependent alterations – e.g., sustained pericontusional hermorrhage [194]. While low-dose norepinephrine (0.15 µg/kg/min) significantly reduced cortical contusion volume, higher dose (0.3 and 1.0 µg/kg/min) did not influence contusion compared to control rats. Pericontusional hemorrhage was significantly increased at all doses, being mostly pronounced at 0.3 and 1.0 µg/kg/min. To limit potential detrimental side effects, CPP should not exceed 120 mmHg which significantly increased cortical contusion volume in rats [193]. In TBI patients, CPP values between 100 and 120 mmHg appeared safe as they did not induce intracranial hypertension in patients with or without vasopressors [195]. It remains to be determined if these adverse effects are caused by elevated hydrostatic pressure due to increased TPR or related to direct, possibly additive norepinephrine-induced pharmacodynamic influences. In cases of intracranial hypertension as investigated experimentally by increasing intracranial volume inflating a balloon [196] or infusing fluid into the cisterna magna [197] cerebral perfusion is impaired and the upper limit of CBF autoregulation is reduced, respectively. Thus, the ICP-dependent narrowing of the cerebral autoregulation interval might increase the risk for norepinephrine-mediated brain injury, as higher norepinephrine dose is required to elevate CPP. Then again, impaired cerebral perfusion might prevent its penetration, thereby reducing the risk of norepinephrine-mediated cell damage.

Traumatic Brain Injury, Norepinephrine, and Inter-Organ Changes

Pharmacokinetics

Plasma norepinephrine is influenced by organ dysfunction. While continuous norepinephrine infusion dose-dependently increases plasma levels [198] in nonseptic TBI patients, septic patients show a significant decrease in norepinephrine clearance resulting in prolonged half-life [199]. This, in turn, could aggravate adrenergic organ damage. To properly control administration of drugs in the critically ill, changes in volume of distribution, elimination half-life, protein binding, clearance, and active metabolites need to be considered on an individual and daily basis to determine the appropriate dose and possibly attenuate developing tolerance [200] and also improve treatment of withdrawal symptoms [201].

Inflammation- and sepsis-mediated encephalopathy

This area comprises a plethora of complex pathophysiological alterations related to microorganisms and their toxins, inflammatory mediators, metabolic disturbances, changes in cerebral perfusion, alterations in amino acid and neurotransmitter homeostasis, and aggravated energy expenditure [202]. In otherwise healthy rats, systemic endotoxemia induces cerebral inflammation [203, 204] but fails to influence cerebral perfusion [205]. In brain-injured rats, sustained systemic inflammation significantly impairs cerebral vascular and metabolic response [206] and aggravates TBI-induced local inflammation [207]. Under these conditions, norepinephrine is of importance as the increased cerebral oxygen consumption and cerebral perfusion are mediated by β-adrenergic activation [208], cerebral norepinephrine uptake and synthesis is impaired [209, 210], and central (brain) as well as peripheral (thrombocytes) α_2-adrenergic transmission is disturbed [211]. While norepinephrine infusion does not adversely affect cerebral perfusion in endotoxemic sheep [212], similar investigations have not yet been performed following TBI with severe inflammation.

Receptor Regulation

Chronic receptor stimulation or inhibition alters receptor affinity and activity due to phosphorylation, posttranscriptional, and posttranslational changes. In this context, prolonged endogenous as well as exogenous catecholamine administration reduces α_2 receptor affinity in human thrombocytes [95] and rat brain [213],

and decreases β_2 receptors in human mononuclear leukocytes [214] which might be influenced by certain genetic predisposition to differential β_2 adrenergic receptor regulation as seen in human lymphocytes [215] and human neutrophils [216]. In critically ill patients, β-adrenergic receptors of circulating lymphocytes are reduced [217] and inflammatory cytokines might impair β-adrenergic receptor-dependent production of the regulatory cAMP [217]. Adrenergic receptors are also influenced by steroids, retinoids, and thyroid hormones at the level of transcription, resulting in a decreased expression of adrenergic receptors in critically ill patients with disturbed hormonal influence. Ensuing arterial hypotension requires steroid substitution to increase sensitivity to α_1 receptor stimulation [218].

Influence of Opioids and Benzodiazepines

Basic treatment of patients suffering from severe TBI includes continuous intravenous infusion of opioids (e.g., fentanyl) and benzodiazepines (e.g., midazolam). Apart from sedation and analgesia, opioids and benzodiazepines can induce tolerance, predispose to withdrawal symptoms, influence thrombocyte and leukocyte functions, and modulate adrenergic responsiveness of smooth muscle cells. Midazolam inhibits norepinephrine release from sympathetic synapses [219] and allosterically modulates α-adrenergic receptors of smooth muscle cells [219, 220]. Midazolam dose-dependently inhibits activation of human thrombocytes [221, 222], reduces thrombocyte–leukocyte interactions [221], inhibits neutrophil apoptosis and monocyte chemotaxis [223, 224], thereby influencing the inflammatory response. Chronic administration of fentanyl inhibits dobutamine-related hemodynamic changes by modulating β-adrenergic receptors [225] and reduces α_1 pulmonary vasoconstriction [18]. In addition, chronic opioids promote astrogliosis which is reduced by α_2 inhibition [226]. Immunosuppressive properties of opioids [227] and α_2-mediated thrombocyte activation are discussed controversially [228–230].

Withdrawal Symptoms

Chronic opioid and benzodiazepine infusion changes function of opioid and adrenergic receptors, thereby promoting drug dependence and disturbed arousal. Ensuing withdrawal symptoms can be modulated pharmacologically by α_2-adrenergic agonists and α_1 and α_2 antagonists to suppress excessive norepinephrine release [231] and activation of the hypothalamus–pituitary–adrenocortical axis [232]. Pharmacological control of withdrawal symptoms, however, is complex as α_2 inhibition (yohimbine) preceeding α_2 stimulation (clonidine) is superior to pretreatment using yohimbine or clonidine alone [233, 234]. Under clinical conditions, opioids and benzodiazepines should be reduced slowly [201]. Arising "sympathetic storm", characterized by hypertension, tachycardia, tachypnea, arousal without adequate responsiveness, sweating, and increased energy expenditure [235] usually requires further sedation. While clonidine is commonly used, newer data suggest its avoidance. An internationally valid concept of which agents to use and how to proceed is still lacking and is strongly needed to avoid interfering with anticipated neuroprotection.

Open Questions for Future Clinical and Experimental Research

Despite its daily use, relatively few data is available related to time-dependent differential influences of norepinephrine-induced and receptor-mediated organ-specific alterations in critically ill patients suffering from severe TBI with and without additional organ dysfunction. To improve current treatment modalities, future research is warranted to address specific questions.

1. Pharmacokinetics and pharmacodynamics
   - Is there a characteristic temporal profile for critically ill patients?
   - Are there differences in complicated (SIRS/ sepsis) vs. noncomplicated cases?
   - Do these changes correlate with systemic and local monitoring parameters?
   - Can changes within the injured brain be assessed by calculating arterio-jugularvenous differences?

2. Systemic and local monitoring
   - Which parameters should be integrated in daily clinical routine?
   - How many measurements are required?
   - Will changes reflect evolving impairment or completed perturbation?

3. Detrimental effects of infused norepinephrine
   - Are potential adverse effects dependent on dose or length of administration?
   - Is activation of thrombocytes and modulation of leukocytes really induced by infused norepinephrine or a mere *in vitro* effect?
   - Does infused norepinephrine promote brain contusion growth and hemorrhage?

4. Disturbed vascular reactivity and autoregulation
   - Does norepinephrine infusion increase the risk of cell damage in case of disturbed vascular reactivity and autoregulation?

- Should other vasoconstricting agents be used when testing autoregulation?
- Is pretreatment with β-blockers essential to prevent impairment of cerebral metabolism upon increasing norepinephrine dose?

5. Induced dependence, tolerance, and withdrawal
   - How should drug dosage be reduced to avoid a surge in norepinephrine release?
   - Is this sustained noradrenergic response detrimental?
   - Does clonidine administration impair anticipated neuroprotection and affect neurorehabilitation processes?
   - Which pharmacological paradigm should be followed to replace clonidine?

6. Pharmacological promotion of norepinephrine-dependent regeneration
   - Can plasticity, regeneration, and neuropsychomnestic deficits be influenced in patients with severe TBI?
   - Which pharmacological compounds should be used?
   - When should administration of these drugs start?

7. Change in therapeutic strategy
   - Will an increase in cerebral metabolism depressing drugs reduce the required norepinephrine dose and thus decrease potential adverse side effects?
   - Will this relate to an improved clinical course and subsequent neurorehabilitation?

References

1. Carrasco GA, Van de Kar LD. Neuroendocrine pharmacology of stress. Eur J Pharmacol 2003;463:235–72.
2. Tsigos C, Chrousos GP. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. J Psychosom Res 2002;53:865–71.
3. Koiv L, Merisalu E, Zilmer K, et al. Changes of sympatho-adrenal and hypothalamo-pituitary-adrenocortical system in patients with head injury. Acta Neurol Scand 1997;96:52–8.
4. Kraut A, Barbiro-Michaely E, Mayevsky A. Differential effects of norepinephrine on brain and other less vital organs detected by a multisite multiparametric monitoring system. Med Sci Monit 2004;10:BR215–20 (Epub 2004 Jun 29).
5. Sakka SG, Meier-Hellmann A, Reinhart K. Do fluid administration and reduction in norepinephrine dose improve global and splanchnic haemodynamics? Br J Anaesth 2000;84:758–62.
6. Keel M, Trentz O. Pathophysiology of polytrauma. Injury 2005;36:691–709.
7. Di Giantomasso D, May CN, Bellomo R. Norepinephrine and vital organ blood flow. Intensive Care Med 2002;28:1804–9.
8. Levy B, Bollaert PE, Charpentier C, Nace L, et al. Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study. Intensive Care Med 1997;23:282–7.
9. Nygren A, Thoren A, Ricksten SE. Effects of norepinephrine alone and norepinephrine plus dopamine on human intestinal mucosal perfusion. Intensive Care Med 2003;29:1322–8.
10. Krouzecky A, Matejovic M, Radej J, et al. Perfusion pressure manipulation in porcine sepsis: effects on intestinal hemodynamics. Physiol Res 2005; (Epub ahead of print).
11. Albanese J, Leone M, Garnier F, et al. Renal effects of norepinephrine in septic and nonseptic patients. Chest 2004;126:534–9.
12. Leon-Velarde F, Bourin MC, Germack R, et al. Differential alterations in cardiac adrenergic signaling in chronic hypoxia or norepinephrine infusion. Am J Physiol Regul Integr Comp Physiol 2001;280:R274–81.
13. Rassler B, Barth W, Zimmer HG. Transient pleural effusion in norepinephrine-stimulated rats. Basic Res Cardiol 2001;96:471–7.
14. Rassler B, Reissig C, Briest W, et al. Catecholamine-induced pulmonary edema and pleural effusion in rats – alpha- and beta-adrenergic effects. Respir Physiol Neurobiol 2003;135:25–37.
15. Communal C, Colucci WS. The control of cardiomyocyte apoptosis via the beta-adrenergic signaling pathways. Arch Mal Coeur Vaiss 2005;98:236–41.
16. Bourgoin A, Leone M, Delmas A, et al. Increasing mean arterial pressure in patients with septic shock: effects on oxygen variables and renal function. Crit Care Med 2005;33:780–6.
17. Kaye AD, Hoover JM, Baber SR, et al. Effects of norepinephrine on alpha-subtype receptors in the feline pulmonary vascular bed. Crit Care Med 2004 ;32:2300–3.
18. Sohn JT, Ding X, McCune DF, et al. Fentanyl attenuates alpha1B-adrenoceptor-mediated pulmonary artery contraction. Anesthesiology 2005;103:327–34.
19. Abraham E. Neutrophils and acute lung injury. Crit Care Med 2003;31:Suppl 4:S195–9.
20. Sautner T, Wessely C, Riegler M, et al. Early effects of catecholamine therapy on mucosal integrity, intestinal blood flow, and oxygen metabolism in porcine endotoxin shock. Ann Surg 1998;228:239–48.
21. De Backer D, Creteur J, Silva E, et al. Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: which is best? Crit Care Med 2003;31:1659–67.
22. Schwarz B, Hofstotter H, Salak N, et al. Effects of norepinephrine and phenylephrine on intestinal oxygen supply and mucosal tissue oxygen tension. Intensive Care Med 2001;27:593–601.
23. Reinelt H, Radermacher P, Kiefer P, et al. Impact of exogenous beta-adrenergic receptor stimulation on hepatosplanchnic oxygen kinetics and metabolic activity in septic shock. Crit Care Med 1999;27:325–31.
24. Guerin JP, Levraut J, Samat-Long C, et al. Effects of dopamine and norepinephrine on systemic and hepatosplanchnic hemodynamics, oxygen exchange, and energy balance in vasoplegic septic patients. Shock 2005;23:18–24.
25. Martikainen TJ, Tenhunen JJ, Uusaro A, et al. The effects of vasopressin on systemic and splanchnic hemodynamics and metabolism in endotoxin shock. Anesth Analg 2003;97:1756–63.
26. Martikainen TJ, Tenhunen JJ, Giovannini I, et al. Epinephrine induces tissue perfusion deficit in porcine endotoxin shock: evaluation by regional CO_2 content gradients and lactate-to-pyruvate ratios. Am J Physiol Gastrointest Liver Physiol 2005;288:G586–92.
27. Schlichtig R, Kramer DJ, Boston JR, et al: Renal O_2 consumption during progressive hemorrhage. J Appl Physiol 1991;70:1957–62.
28. Ba ZF, Wang P, Koo DJ, et al. Alterations in tissue oxygen consumption and extraction after trauma and hemorrhagic shock. Crit Care Med 2000;28:2837–42.
29. Rajapakse NW, Oliver JJ, Evans RG. Nitric oxide in responses of regional kidney blood flow to vasoactive agents in anesthetized rabbits. J Cardiovasc Pharmacol 2002;40:210–9.

30. Richer M, Robert S, Lebel M. Renal hemodynamics during norepinephrine and low-dose dopamine infusions in man. Crit Care Med 1996;24:1150–6.
31. Booke M, Hinder F, McGuire R, et al. Noradrenaline and nomega-monomethyl-L-arginine (L-NMMA): effects on haemodynamics and regional blood flow in healthy and septic sheep. Clin Sci (Lond) 2000;98:193–200.
32. Morimatsu H, Uchino S, Chung J, et al. Norepinephrine for hypotensive vasodilatation after cardiac surgery: impact on renal function. Intensive Care Med 2003;29:1106–12.
33. Van Hall G, Steensberg A, Sacchetti M, et al. Interleukin-6 stimulates lipolysis and fat oxidation in humans. J Clin Endocrinol Metab 2003;88:3005–10.
34. Lafontan M, Barbe P, Galitzky J, et al. Adrenergic regulation of adipocyte metabolism. Hum Reprod 1997;12:Suppl 1:6–20.
35. Qvisth V, Hagstrom-Toft E, Enoksson S, et al. Human skeletal muscle lipolysis is more responsive to epinephrine than to norepinephrine stimulation in vivo. J Clin Endocrinol Metab 2005; (Epub ahead of print).
36. Mitch WE, Price SR. Mechanisms activating proteolysis to cause muscle atrophy in catabolic conditions. J Ren Nutr 2003;13:149–52.
37. Watford M. Not all injury-induced muscle proteolysis is due to increased activity of the ubiquitin/proteasome system: evidence for up-regulation of macrophage-associated lysosomal proteolysis in a model of local trauma. Nutr Rev 2003;61:34–8.
38. Hasselgren PO, Fischer JE. Counter-regulatory hormones and mechanisms in amino acid metabolism with special reference to the catabolic response in skeletal muscle. Curr Opin Clin Nutr Metab Care 1999;2:9–14.
39. Hasselgren PO, Wray C, Mammen J. Molecular regulation of muscle cachexia: it may be more than the proteasome. Biochem Biophys Res Commun 2002;290:1–10.
40. Rooyackers OE, Nair KS. Hormonal regulation of human muscle protein metabolism. Annu Rev Nutr 1997;17:457–85.
41. Navegantes LC, Resano NM, Baviera AM, et al. CL 316,243, a selective beta(3)-adrenergic agonist, inhibits protein breakdown in rat skeletal muscle. Pflugers Arch 2005; (Epub ahead of print).
42. Garcia-Barrado MJ, Sancho C, Palomero J, et al. Role of alpha2-adrenoceptors on the hyperglycaemic and insulin secretory effects derived from alpha1- and beta-adrenoceptor stimulation in the rabbit. J Auton Pharmacol 1998;18:287–95.
43. Van den Berghe G. How does blood glucose control with insulin save lives in intensive care? J Clin Invest 2004;114:1187–95.
44. Stover JF, Sakowitz OW, Schoning B, et al. Norepinephrine infusion increases interleukin-6 in plasma and cerebrospinal fluid of brain-injured rats. Med Sci Monit 2003;9:382–8.
45. Filipponi P, Marcelli M, Nicoletti I, et al. Characterization of adrenergic control of glucagon secretion from isolated perfused rat pancreas. Diabetes Metab 1982;8:313–8
46. Hirose H, Maruyama H, Itoh K, et al. Alpha-2 adrenergic agonism stimulates islet glucagon release from perfused rat pancreas: possible involvement of alpha-2A adrenergic receptor subtype. Acta Endocrinol (Copenh) 1992;127:279–83.
47. Kreisman SH, Ah Mew N, Halter JB, et al. Norepinephrine infusion during moderate-intensity exercise increases glucose production and uptake. J Clin Endocrinol Metab 2001;86:2118–24.
48. Jeremitsky E, Omert LA, Dunham CM, et al. The impact of hyperglycemia on patients with severe brain injury. J Trauma 2005; 58:47–50.
49. Ensinger H, Weichel T, Lindner KH, et al. Effects of norepinephrine, epinephrine, and dopamine infusions on oxygen consumption in volunteers. Crit Care Med 1993;21:1502–8.
50. McCarter FD, James JH, Luchette FA, et al. Adrenergic blockade reduces skeletal muscle glycolysis and Na(+), K(+)-ATPase activity during hemorrhage. J Surg Res 2001;99:235–44.
51. Hang CH, Shi JX, Li JS, et al. Up-regulation of intestinal nuclear factor kappa B and intercellular adhesion molecule-1 following traumatic brain injury in rats. World J Gastroenterol 2005 28;11:1149–54.
52. Hang CH, Shi JX, Li JS, et al. Expressions of intestinal NF-kappaB, TNF-alpha, and IL-6 following traumatic brain injury in rats. J Surg Res 2005;123:188–93.
53. Benschop RJ, Rodriguez-Feuerhahn M, Schedlowski M. Catecholamine-induced leukocytosis: early observations, current research, and future directions. Brain Behav Immun 1996;10:77–91.
54. Stevenson JR, Westermann J, Liebmann PM, et al. Prolonged alpha-adrenergic stimulation causes changes in leukocyte distribution and lymphocyte apoptosis in the rat. J Neuroimmunol 2001;120:50–57.
55. Chao HJ, Hsu YC, Yuan HP, et al. The conditioned enhancement of neutrophil activity is catecholamine dependent. J Neuroimmunol 2005;158:159–69.
56. Miksa M, Wu R, Zhou M, et al. Sympathetic excitotoxicity in sepsis: pro-inflammatory priming of macrophages by norepinephrine. Front Biosci 20051;10:2217–29.
57. Kohm AP, Sanders VM. Norepinephrine and b2-adrenergic receptor stimulation regulate CD4+ T and B lymphocyte function in vitro and in vivo. Pharmacol Rev 2001;53:487–525.
58. Menges T, Engel J, Welters I, et al. Changes in blood lymphocyte populations after multiple trauma: association with posttraumatic complications. Crit Care Med 1999;27:733–40.
59. Takabayashi A, Kanai M, Kawai Y, et al. Change in mitochondrial membrane potential in peripheral blood lymphocytes, especially in natural killer cells, is a possible marker for surgical stress on the immune system. World J Surg 2003;27:659–65.
60. Gan X, Zhang L, Solomon GF, et al. Mechanism of norepinephrine-mediated inhibition of human NK cytotoxic functions: inhibition of cytokine secretion, target binding, and programming for cytotoxicity. Brain Behav Immun 2002;16:227–46.
61. Elenkov IJ, Wilder RL, Chrousos GP, et al. The sympathetic nerve – an integrative interface between two supersystems: the brain and the immune system. Pharmacol Rev 2000;52:595–638.
62. Lünemann JD, et al. Effects of norepinephrine on oxygen consumption of quiescent and activated human peripheral blood mononuclear cells. Ann NY Acad Sci 2002;966:365–8.
63. Garcia JJ, del Carmen Saez M, De la Fuente M, et al. Noradrenaline and its end metabolite 3-methoxy-4-hydroxyphenylglycol inhibit lymphocyte chemotaxis: role of alpha- and beta-adrenoreceptors. Mol Cell Biochem 2003;254:305–9.
64. Maestroni GJ. Adrenergic modulation of dendritic cells function: relevance for the immune homeostasis. Curr Neurovasc Res 2005;2:169–73.
65. Uusaro A, Russell JA. Could anti-inflammatory actions of catecholamines explain the possible beneficial effects of supranormal oxygen delivery in critically ill surgical patients? Intensive Care Med 2000;26:299–304.
66. Madrigal JL, Feinstein DL, Dello Russo C. Norepinephrine protects cortical neurons against microglial-induced cell death. J Neurosci Res 2005;81:390–6.
67. Klotz L, Sastre M, Kreutz A, et al. Noradrenaline induces expression of peroxisome proliferator activated receptor gamma (PPARgamma) in murine primary astrocytes and neurons. J Neurochem 2003;86:907–16.
68. Bergmann M, Sautner T. Immunomodulatory effects of vasoactive catecholamines. Wien Klin Wochenschr 2002;114:752–61

69. Gavrilyuk V, Dello Russo C, Heneka MT, et al. Norepinephrine increases I kappa B alpha expression in astrocytes. J Biol Chem 2002;277:29662–8.
70. Kuroki K, Takahashi HK, Iwagaki H, et al. Beta2-adrenergic receptor stimulation-induced immunosuppressive effects possibly through down-regulation of co-stimulatory molecules, ICAM-1, CD40 and CD14 on monocytes. J Int Med Res 2004;32:465–83.
71. Galea E, Heneka MT, Dello Russo C, et al. Intrinsic regulation of brain inflammatory responses. Cell Mol Neurobiol. 2003 Oct;23:625-35.
72. Esmon CT. Interactions between the innate immune and blood coagulation systems. TRENDS in Immunology 2004;25.
73. Weyrich AS, et al. The evolving role of platelets in inflammation. J Thrombo Haemost 2003;1:1897–905.
74. Falcinelli E, Guglielmini G, Torti M, et al. Intraplatelet signaling mechanisms of the priming effect of matrix metalloproteinase-2 on platelet aggregation. J Thromb Haemost. 2005;3:2526–35.
75. Gibbins JM. Platelet adhesion signalling and the regulation of thrombus formation. J cell Sci 2004;117:3415—25.
76. Cambien B, et al. Antithrombotic activity of TNF-α. J Clin Invest 2003;112:1589–96.
77. Kirschenbaum LA, Aziz M, Astiz ME, et al. Influence of rheologic changes and platelet-neutrophil interactions on cell filtration in sepsis. Am J Respir Crit Care Med 2000;161:1602–7.
78. Esposito CJ, Popescu WM, Rinder HM, et al. Increased leukocyte-platelet adhesion in patients with graft occlusion after peripheral vascular surgery. Thromb Haemost 2003;90:1128–34.
79. Strange C, Gottehrer A, Birmingham K, et al. Platelets attenuate oxidant-induced permeability in endothelial monolayers: glutathione-dependent mechanisms. J Appl Physiol 1996;81:1701–6.
80. Ueno H, Hirasawa H, Oda S, et al. Coagulation/fibrinolysis abnormality and vascular endothelial damage in the pathogenesis of thrombocytopenic multiple organ failure. Crit Care Med 2002;30:2242–8.
81. Whalen MJ, Carlos TM, Dixon CE, et al. Reduced brain edema after traumatic brain injury in mice deficient in P-selectin and intercellular adhesion molecule-1. J Leukoc Biol 2000;67:160–8.
82. Mhatre M, Nguyen A, Kashani S, et al. Thrombin, a mediator of neurotoxicity and memory impairment. Neurobiol Aging 2004;25:783–93.
83. Lu D, Mahmood A, Goussev A, et al. Atorvastatin reduction of intravascular thrombosis, increase in cerebral microvascular patency and integrity, and enhancement of spatial learning in rats subjected to traumatic brain injury. J Neurosurg 2004;101:813–21.
84. Endo S, Inada K, Kasai T, et al. Levels of soluble adhesion molecules and cytokines in patients with septic multiple organ failure. J Inflamm 1995–1996;46:212–9.
85. Gawaz M, Fateh-Moghadam S, Pilz G, et al. Platelet activation and interaction with leucocytes in patients with sepsis or multiple organ failure. Eur J Clin Invest 1995;25:843–51.
86. Boldt J, Muller M, Kuhn D, et al. Circulating adhesion molecules in the critically ill: a comparison between trauma and sepsis patients. Intensive Care Med 1996;22:122–8.
87. Jacoby RC, Owings JT, Holmes J, et al. Platelet activation and function after trauma. J Trauma 2001;51:639–47.
88. Russwurm S, Vickers J, Meier-Hellmann A, et al. Platelet and leukocyte activation correlate with the severity of septic organ dysfunction. Shock 2002;17:263–8.
89. Bunescu A, Widman J, Lenkei R, et al. Increases in circulating levels of monocyte-platelet and neutrophil-platelet complexes following hip arthroplasty. Clin Sci (Lond) 2002;102:279–86.
90. Gawaz M, Dickfeld T, Bogner C, et al. Platelet function in septic multiple organ dysfunction syndrome. Intensive Care Med 1997;23:379–85.
91. Kirschenbaum LA, Adler D, Astiz ME, et al. Mechanisms of platelet-neutrophil interactions and effects on cell filtration in septic shock. Shock 2002;17:508–12.
92. Kirschenbaum LA, McKevitt D, Rullan M, et al. Importance of platelets and fibrinogen in neutrophil-endothelial cell interactions in septic shock. Crit Care Med 2004;32:1904–9.
93. Horn et al. Epinephrine enhances platelet-neutrophil adhesion in whole blood in vitro. Anesth Analg 2005;100:520– 6.
94. Hikasa Y, et al. Effects of imidazoline and non-imidazoline α-adrenergic agents on canine platelet aggregation. Pharmacology 1999;58:171–82.
95. Ikarugi H, Taka T, Nakajama S, et al. Norepinephrine, but not epinephrine, enhances platelet reactivity and coagulation after exercise in humans. J Appl Physiol 1999;86:133–8.
96. Hollister AS, Fitzgerald GA, Nadeau JH, et al. Acute reduction in human platelet α2-adrenoreceptor affinity for agonist by endogenous and exogenous catecholamines. J Clin Invest 1983;72:1498–505.
97. Pinthing D, Songsermsakul, Rattanachamnong P, et al. The effects of imidazoline agents on the aggregation of human platelets. JPP 2004;56:213–20.
98. Alt E, Amann-Vesti BR, Madl C, et al. Platelet aggregation and blood rheology in severe sepsis/septic shock: relation to the Sepsis-related Organ Failure Assessment (SOFA) score. Clin Hemorheol Microcirc 2004;30:107–15.
99. Vanderschueren S, et al. Thrombocytopenia and prognosis in intensive care. Crit Care Med 2000;28:1871–6.
100. Berridge CW, Waterhouse BD. The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Res Brain Res Rev 2003;42:33–84.
101. Gibbs ME, Summers RJ. Alpha 2-adrenoceptors in the basal ganglia have a role in memory consolidation and reinforcement. Neuropharmacology 2003;45:355–67.
102. Knox D, Sarter M, Berntson GG. Visceral afferent bias on cortical processing: role of adrenergic afferents to the basal forebrain cholinergic system. Behav Neurosci 2004;118:1455–9.
103. Murchison CF, Zhang XY, Zhang WP, et al. A distinct role for norepinephrine in memory retrieval. Cell. 2004;117:131–43.
104. Arnsten AF, Li BM. Neurobiology of executive functions: catecholamine influences on prefrontal cortical functions. Biol Psychiatry 2005;57:1377–84.
105. Devoto P, Flore G, Saba P, et al. Stimulation of the locus coeruleus elicits noradrenaline and dopamine release in the medial prefrontal and parietal cortex. J Neurochem 2005;92:368–74.
106. Jurgens CW, Rau KE, Knudson CA, et al. Beta1 adrenergic receptor-mediated enhancement of hippocampal CA3 network activity. J Pharmacol Exp Ther 2005;314:552–60 (Epub 2005 May 20).
107. Riba J, Rodriguez-Fornells A, Morte A, et al. Noradrenergic stimulation enhances human action monitoring. J Neurosci 2005;25:4370–4.
108. Yavich L, Jakala P, Tanila H. Noradrenaline overflow in mouse dentate gyrus following locus coeruleus and natural stimulation: real-time monitoring by in vivo voltammetry. J Neurochem 2005;95:641–50.
109. Nieuwenhuis S, Aston-Jones G, Cohen JD. Decision making, the P3, and the locus coeruleus-norepinephrine system. Psychol Bull 2005;131:510–32.
110. Otmakhova NA, Lewey J, Asrican B, et al. Inhibition of perforant path input to the CA1 region by serotonin and noradrenaline. J Neurophysiol 2005;94:1413–22 (Epub 2005 May 11).
111. Gupta BB, Spessert R, Vollrath L. Molecular components and mechanism of adrenergic signal transduction in mammalian pineal gland: regulation of melatonin synthesis. Indian J Exp Biol 2005;43:115–49.

112. Forray MI, Gysling K. Role of noradrenergic projections to the bed nucleus of the stria terminalis in the regulation of the hypothalamic-pituitary-adrenal axis. Brain Res Brain Res Rev 2004;47 :145–60.
113. Grange-Messent V, Raison D, Dugas B, et al. Noradrenaline upregulates the neuronal and the inducible nitric oxide synthase isoforms in magnocellular neurons of rat brain slices. J Neurosci Res 2004;78:683–90.
114. Iqbal J, Manley TR, Yue Q, et al. Noradrenergic regulation of hypothalamic cells that produce growth hormone-releasing hormone and somatostatin and the effect of altered adiposity in sheep. J Neuroendocrinol 2005;17:341–52.
115. Li DP, Atnip LM, Chen SR, et al. Regulation of synaptic inputs to paraventricular-spinal output neurons by alpha2 adrenergic receptors. J Neurophysiol 2005;93:393–402.
116. Hayward LF. Evidence for alpha-2 adrenoreceptor modulation of arterial chemoreflexes in the caudal solitary nucleus of the rat. Am J Physiol Regul Integr Comp Physiol 2001;281:R1464–73.
117. Viemari JC, Ramirez JM. Norepinephrine differentially modulates different types of respiratory pacemaker and non-pacemaker neurons. J Neurophysiol 2006; (Epub ahead of print).
118. Rogers RC, Travagli RA, Hermann GE. Noradrenergic neurons in the rat solitary nucleus participate in the esophageal-gastric relaxation reflex. Am J Physiol Regul Integr Comp Physiol 2003;285:R479–89.
119. Collier TJ, Greene JG, Felten DL, et al. Reduced cortical noradrenergic neurotransmission is associated with increased neophobia and impaired spatial memory in aged rats. Neurobiol Aging 2004;25:209–21.
120. Noh JS, Kim EY, Kang JS, et al. Neurotoxic and neuroprotective actions of catecholamines in cortical neurons. Exp Neurol 1999;159:217–24.
121. Troadec JD, Marien M, Darios F, et al. Noradrenaline provides long-term protection to dopaminergic neurons by reducing oxidative stress. J Neurochem 2001;79:200–10.
122. Traver S, Salthun-Lassalle B, Marien M, et al. The neurotransmitter noradrenaline rescues septal cholinergic neurons in culture from degeneration caused by low-level oxidative stress. Mol Pharmacol 2005;67:1882–91 (Epub 2005 Mar 22).
123. Gordon GR, Baimoukhametova DV, Hewitt SA, et al. Norepinephrine triggers release of glial ATP to increase postsynaptic efficacy. Nat Neurosci 2005;8:1078–86 (Epub 2005 Jul 3).
124. Amtage F, Neughebauer B, McIntosh JM, et al. Characterization of nicotinic receptors inducing noradrenaline release and absence of nicotinic autoreceptors in human neocortex. Brain Res Bull 2004;62:413–23.
125. Koga H, Ishibashi H, Shimada H, et al. Activation of presynaptic GABA-A receptors increases spontaneous glutamate release onto noradrenergic neurons of the rat locus coeruleus. Brain Res 2005;1046:24–31.
126. Egli RE, Kash TL, Choo K, et al. Norepinephrine modulates glutamatergic transmission in the bed nucleus of the stria terminalis. Neuropsychopharmacology 2005;30:657–68.
127. Timmons SD, Geisert E, Stewart AE, et al. Alpha2-adrenergic receptor-mediated modulation of calcium current in neocortical pyramidal neurons. Brain Res 2004;1014:184–96.
128. Paladini CA, Williams JT. Noradrenergic inhibition of midbrain dopamine neurons. J Neurosci 2004;24:4568–75.
129. Pan WH, Yang SY, Lin SK. Neurochemical interaction between dopaminergic and noradrenergic neurons in the medial prefrontal cortex. Synapse. 2004;53:44–52.
130. Milusheva EA, Baranyi M. Implication of ionotropic glutamate receptors in the release of noradrenaline in hippocampal CA1 and CA3 subregions under oxygen and glucose deprivation. Neurochem Int 2003;43:543–50.
131. Stevens DR, Kuramasu A, Eriksson KS, et al. Alpha 2-adrenergic receptor-mediated presynaptic inhibition of GABAergic IPSPs in rat histaminergic neurons. Neuropharmacology 2004;46:1018–22.
132. Hansson E, Ronnback L. Adrenergic receptor regulation of amino acid neurotransmitter uptake in astrocytes. Brain Res Bull 1992;29:297–301.
133. Cohen Z, Molinatti G, Hamel E. Astroglial and vascular interactions of noradrenaline terminals in the rat cerebral cortex. J Cereb Blood Flow Metab 1997;17:894–904.
134. Mulligan SJ, MacVicar BA. Calcium transients in astrocyte endfeet cause cerebrovascular constrictions. Nature 2004; 431:195–9.
135. Lee TJ. Sympathetic modulation of nitrergic neurogenic vasodilation in cerebral arteries. Jpn J Pharmacol 2002; 88:26–31.
136. Hardebo JE, Owman C. Barrier mechanisms for neurotransmitter monoamines and their precursors at the blood-brain interface. Ann Neurol 1980;8:1–31.
137. Ohtsuki S. New aspects of the blood-brain barrier transporters; physiological roles in the central nervous system. Biol Pharm Bull 2004;27:1489–96.
138. Borges N, Shi F, Azevedo I, et al. Changes in brain microvessel endothelial cell monolayer permeability induced by adrenergic drugs. Eur J Pharmacol 1994;269:243–8.
139. Tsacopoulos M, Magistretti PJ. Metabolic coupling between glia and neurons. J Neurosci 1996;16:877–85.
140. Allaman I, Pellerin L, Magistretti PJ. Protein targeting to glycogen mRNA expression is stimulated by noradrenaline in mouse cortical astrocytes. Glia 2000;30:382–91.
141. Fillenz M, Lowry JP, Boutelle MG, et al. The role of astrocytes and noradrenaline in neuronal glucose metabolism. Acta Physiol Scand 1999;167:275–84.
142. Huang R, Hertz L. Noradrenaline-induced stimulation of glutamine metabolism in primary cultures of astrocytes. J Neurosci Res 1995;41:677–83.
143. Pierre K, Debernardi R, Magistretti PJ, et al. Noradrenaline enhances monocarboxylate transporter 2 expression in cultured mouse cortical neurons via a translational regulation. J Neurochem 2003;86:1468–76.
144. Molina PE, Abumrad NN. Contribution of excitatory amino acids to hypoglycemic counter-regulation. Brain Res 2001;899:201–8.
145. Beverly JL, de Vries MG, Beverly MF, et al. Norepinephrine mediates glucoprivic-induced increase in GABA in the ventromedial hypothalamus of rats. Am J Physiol Regul Integr Comp Physiol 2000;279:R990–6.
146. de Vries MG, Lawson MA, Beverly JL. Hypoglycemia-induced noradrenergic activation in the VMH is a result of decreased ambient glucose. Am J Physiol Regul Integr Comp Physiol 2005;289:R977–81.
147. Gu Q. Neuromodulatory transmitter systems in the cortex and their role in cortical plasticity. Neuroscience 2002;111:815–35.
148. Laifenfeld D, Klein E, Ben-Shachar D. Norepinephrine alters the expression of genes involved in neuronal sprouting and differentiation: relevance for major depression and antidepressant mechanisms. J Neurochem 2002;83:1054–64.
149. Heneka MT, Gavrilyuk V, Landreth GE, et al. Noradrenergic depletion increases inflammatory responses in brain: effects on IkappaB and HSP70 expression. J Neurochem 2003;85:387–98.
150. Payen D, Quintin L, Plaisance P, et al. Head injury: clonidine decreases plasma catecholamines. Crit Care Med 1990;18:392–5.

151. Feeney DM, De Smet AM, Rai S. Noradrenergic modulation of hemiplegia: facilitation and maintenance of recovery. Restor Neurol Neurosci 2004;22:175–90.
152. Dunn-Meynell AA, Yarlagadda Y, Levin BE. Alpha 1-adrenoceptor blockade increases behavioral deficits in traumatic brain injury. J Neurotrauma 1997;14:43–52.
153. Dunn-Meynell AA, Hassanain M, Levin BE. Norepinephrine and traumatic brain injury: a possible role in post-traumatic edema. Brain Res 1998;800:245–52.
154. Fujinaka T, Kohmura E, Yuguchi T, et al. The morphological and neurochemical effects of diffuse brain injury on rat central noradrenergic system. Neurol Res 2003;25:35–41.
155. Tuor UI, Edvinsson L, McCulloch J. Catecholamines and the relationship between cerebral blood flow and glucose use. Am J Physiol 1986;251:H824–33.
156. Shibata M, Einhaus S, Schweitzer JB, et al. Cerebral blood flow decreased by adrenergic stimulation of cerebral vessels in anesthetized newborn pigs with traumatic brain injury. J Neurosurg 1993;79:696–704.
157. Goldstein LB, Bullman S. Effects of dorsal noradrenergic bundle lesions on recovery after sensorimotor cortex injury. Pharmacol Biochem Behav 1997;58:1151–7.
158. Kikuchi K, Nishino K, Ohyu H. Increasing CNS norepinephrine levels by the precursor L-DOPS facilitates beam-walking recovery after sensorimotor cortex ablation in rats. Brain Res 2000;860:130–5.
159. Zhu J, Hamm RJ, Reeves TM, et al. Postinjury administration of L-deprenyl improves cognitive function and enhances neuroplasticity after traumatic brain injury. Exp Neurol 2000; 166:136–52.
160. Galeotti N, Bartolini A, Ghelardini C. Alpha-2 agonist-induced memory impairment is mediated by the alpha-2A-adrenoceptor subtype. Behav Brain Res 2004;153:409–17.
161. Stibick DL, Feeney DM. Enduring vulnerability to transient reinstatement of hemiplegia by prazosin after traumatic brain injury. J Neurotrauma 2001;18:303–12.
162. Nordstrom CH. Physiological and biochemical principles underlying volume-targeted therapy–the "Lund concept". Neurocrit Care 2005;2:83–95.
163. Napolitano E, Elovic EP, Qureshi AI. Pharmacological stimulant treatment of neurocognitive and functional deficits after traumatic and non-traumatic brain injury. Med Sci Monit 2005;11(6): RA212–20.
164. Wroblewski BA, Joseph AB, Cornblatt RR. Antidepressant pharmacotherapy and the treatment of depression in patients with severe traumatic brain injury: a controlled, prospective study. J Clin Psychiatry 1996;57:582–7.
165. Kanetani K, Kimura M, Endo S. Therapeutic effects of milnacipran (serotonin noradrenalin reuptake inhibitor) on depression following mild and moderate traumatic brain injury. J Nippon Med Sch 2003;70:313–20.
166. Kraus MF, Smith GS, Butters M, et al. Effects of the dopaminergic agent and NMDA receptor antagonist amantadine on cognitive function, cerebral glucose metabolism and D2 receptor availability in chronic traumatic brain injury: a study using positron emission tomography (PET). Brain Inj 2005;19:471–9.
167. Invernizzi RW, Garattini S.Role of presynaptic alpha2-adrenoceptors in antidepressant action: recent findings from microdialysis studies. Prog Neuropsychopharmacol Biol Psychiatry 2004;28:819–27.
168. Garcia AS, Barrera G, Burke TF, et al. Autoreceptor-mediated inhibition of norepinephrine release in rat medial prefrontal cortex is maintained after chronic desipramine treatment. J Neurochem 2004;91:683–93.
169. Tordera RM, Pei Q, Sharp T. Evidence for increased expression of the vesicular glutamate transporter, VGLUT1, by a course of antidepressant treatment. J Neurochem 2005;94:875–83.
170. Zarrindast MR, Ghiasvand M, Homayoun H, et al. Adrenoceptor mechanisms underlying imipramine-induced memory deficits in rats. J Psychopharmacol 2003;17:83–8.
171. Laudenbach V, Mantz J, Lagercrantz H, et al. Effects of alpha(2)-adrenoceptor agonists on perinatal excitotoxic brain injury: comparison of clonidine and dexmedetomidine. Anesthesiology 2002;96:134–41.
172. Stover JF, Steiger P, Stocker R. Treating intracranial hypertension in patients with severe traumatic brain injury during neurointensive care. Eur J Trauma 2005;31:308– 30.
173. Martin NA, Patwardhan RV, Alexander MJ, et al. Characterization of cerebral hemodynamic phases following severe head trauma: hypoperfusion, hyperemia, and vasospasm. J Neurosurg 1997;87:9–19.
174. Vespa P, Bergsneider M, Hattori N, et al. Metabolic crisis without brain ischemia is common after traumatic brain injury: a combined microdialysis and positron emission tomography study. J Cereb Blood Flow Metab 2005;25:763–74.
175. Hattori N, Huang SC, Wu HM, et al. Acute changes in regional cerebral (18)F-FDG kinetics in patients with traumatic brain injury. J Nucl Med 2004;45:775– 83.
176. Hlatky R, Furuya Y, Valadka AB,et al. Dynamic autoregulatory response after severe head injury. J Neurosurg 2002; 97:1054–61.
177. Kroppenstedt SN, Thomale UW, Griebenow M, et al. Effects of early and late intravenous norepinephrine infusion on cerebral perfusion, microcirculation, brain-tissue oxygenation, and edema formation in brain-injured rats. Crit Care Med 2003;31:2211–21.
178. Mascia L, Andrews PJ, McKeating EG, et al. Cerebral blood flow and metabolism in severe brain injury: the role of pressure autoregulation during cerebral perfusion pressure management. Intensive Care Med 2000;26:202–5.
179. MacKenzie ET, McCulloch J, Harper AM. Influence of endogenous norepinephrine on cerebral blood flow and metabolism. Am J Physiol 1976;231:489–94.
180. Berntman L, Dahlgren N, Siesjo BK. Influence of intravenously administered catecholamines on cerebral oxygen consumption and blood flow in the rat. Acta Physiol Scand 1978;104:101–8.
181. Rogers AH, Armstead WM, Mirro R, et al. Influence of intraarterial norepinephrine on cerebral hemodynamics of newborn pigs. Proc Soc Exp Biol Med 1989;191:174–8.
182. Myburgh JA, Upton RN, Grant C. The effect of infusions of adrenaline, noradrenaline and dopamine on cerebral autoregulation under propofol anaesthesia in an ovine model. Intensive Care Med 2003;29:817–24.
183. Edvinsson L, Lacombe P, Owman C, et al. Quantitative changes in regional cerebral blood flow of rats induced by alpha- and beta-adrenergic stimulants. Acta Physiol Scand 1979;107:289–96.
184. Lasbennes F, Lacombe P, Seylaz J. Effect of monoamine oxidase inhibition on the regional cerebral blood flow response to circulating noradrenaline. Brain Res 1988;454:205–11.
185. Unterberg AW, Stover J, Kress B, et al. Edema and brain trauma. Neuroscience 2004;129:1021–9.
186. Mautes AE, Muller M, Cortbus F, et al. Homburg Traumatic Injury Group (HOTBIG). Alterations of norepinephrine levels in plasma and CSF of patients after traumatic brain injury in relation to disruption of the blood-brain barrier. Acta Neurochir (Wien) 2001;143:51–7, discussion 57–8.
187. Kroppenstedt SN, Sakowitz OW, Thomale UW, et al. Influence of norepinephrine and dopamine on cortical perfusion, EEG

activity, extracellular glutamate, and brain edema in rats after controlled cortical impact injury. J Neurotrauma 2002; 19:1421–32.
188. Lang EW, Czosnyka M, Mehdorn HM. Tissue oxygen reactivity and cerebral autoregulation after severe traumatic brain injury. Crit Care Med 2003;31:267–71.
189. Steiner LA, Coles JP, Johnston AJ, et al. Responses of posttraumatic pericontusional cerebral blood flow and blood volume to an increase in cerebral perfusion pressure. J Cereb Blood Flow Metab 2003;23:1371–7.
190. Johnston AJ, Steiner LA, Coles JP, et al. Effect of cerebral perfusion pressure augmentation on regional oxygenation and metabolism after head injury. Crit Care Med 2005;33:189–95, discussion 255–7.
191. Coles JP, Steiner LA, Johnston AJ, et al. Does induced hypertension reduce cerebral ischaemia within the traumatized human brain? Brain 2004;127:2479–90 (Epub 2004 Sep 29).
192. Ogita H, Liao J. Endothelial function and oxidative stress. Endothelium 2004;11:123–32.
193. Kroppenstedt SN, Kern M, Thomale UW, et al. Effect of cerebral perfusion pressure on contusion volume following impact injury. J Neurosurg 1999;90:520–6.
194. Van Landeghem FK, Schreiber S, Unterberg AW, et al. Differential concentration-dependent effects of prolonged norepinephrine infusion on intraparenchymal hemorrhage and cortical contusion in brain-injured rats. J Neurotrauma 2003;20:1327–37.
195. Rosner MJ, Rosner SD, Johnson AH. Cerebral perfusion pressure: management protocol and clinical results. J Neurosurg 1995;83:949–62.
196. Burger R, Bendszus M, Vince GH, et al. A new reproducible model of an epidural mass lesion in rodents. Part I: Characterization by neurophysiological monitoring, magnetic resonance imaging, and histopathological analysis. J Neurosurg 2002;97:1410–8.
197. Hauerberg J, Xiaodong M, Willumsen L, et al. The upper limit of cerebral blood flow autoregulation in acute intracranial hypertension. J Neurosurg Anesthesiol 1998;10:106–12.
198. Johnston AJ, Steiner LA, O'Connell M, et al. Pharmacokinetics and pharmacodynamics of dopamine and norepinephrine in critically ill head-injured patients. Intensive Care Med 2004;30:45–50 (Epub 2003 Oct 29).
199. Beloeil H, Mazoit JX, Benhamou D, et al. Norepinephrine kinetics and dynamics in septic shock and trauma patients. Br J Anaesth 2005;95:782–8 (Epub 2005 Oct 14).
200. Barr J, Donner A. Optimal intravenous dosing strategies for sedatives and analgesics in the intensive care unit. Crit Care Clin 1995;11:827–47.
201. Ducharme C, Carnevale FA, Clermont MS, et al. A prospective study of adverse reactions to the weaning of opioids and benzodiazepines among critically ill children. Intensive Crit Care Nurs 2005;21:179–86 (Epub 2005 Jan 18).
202. Bruder N, Raynal M, Pellissier D, et al. Influence of body temperature, with or without sedation, on energy expenditure in severe head-injured patients. Crit Care Med 1998 Mar;26:568–72.
203. Laflamme N, Rivest S. Effects of systemic immunogenic insults and circulating proinflammatory cytokines on the transcription of the inhibitory factor kappaB alpha within specific cellular populations of the rat brain. J Neurochem 1999;73:309–21.
204. Bohatschek M, Werner A, Raivich G. Systemic LPS injection leads to granulocyte influx into normal and injured brain: effects of ICAM-1 deficiency. Exp Neurol 2001;172:137–52.
205. Law WR, Ferguson JL. Effect of naloxone on regional cerebral blood flow during endotoxin shock in conscious rats. Am J Physiol 1987;253:R425–33.
206. Stubbe HD, Greiner C, Van Aken H, et al. Cerebral vascular and metabolic response to sustained systemic inflammation in ovine traumatic brain injury. J Cereb Blood Flow Metab 2004;24:1400–8.
207. Hang CH, Shi JX, Tian J, et al. Effect of systemic LPS injection on cortical NF-kappaB activity and inflammatory response following traumatic brain injury in rats. Brain Res 2004; 1026:23–32.
208. Westerlind A, Larsson LE, Haggendal J, et al. Effects of propranolol pretreatment on cerebral blood flow, oxygen uptake and catecholamines during metabolic acidosis following E. coli endotoxin in dogs. Acta Anaesthesiol Scand 1995;39:467–71.
209. Freund HR, Muggia-Sullam M, Peiser J, et al. Brain neurotransmitter profile is deranged during sepsis and septic encephalopathy in the rat. J Surg Res 1985;38:267–71.
210. Mizock BA, Sabelli HC, Dubin A, et al. Septic encephalopathy. Evidence for altered phenylalanine metabolism and comparison with hepatic encephalopathy. Arch Intern Med 1990;150:443–9.
211. Hikasa Y, Fukui H, Sato Y, et al. Platelet and brain alpha 2-adrenoceptors and cardiovascular sensitivity to agonists in dogs suffering from endotoxic shock. Fundam Clin Pharmacol 1998; 12:498–509.
212. Booke M, Westphal M, Hinder F, et al. Cerebral blood flow is not altered in sheep with Pseudomonas aeruginosa sepsis treated with norepinephrine or nitric oxide synthase inhibition. Anesth Analg 2003;96:1122–8.
213. Giralt MT, Garcia-Sevilla JA. Acute and long-term regulation of brain alpha 2-adrenoceptors after manipulation of noradrenergic transmission in the rat. Eur J Pharmacol 1989;164:455–66.
214. Tittelbach V, Volff JN, Giray J, et al. Agonist-induced down-regulation of the beta2-adrenoceptor and its mRNA in human mononuclear leukocytes. Biochem Pharmacol 1998;56:967–75.
215. Oostendorp J, Postma DS, Volders H, et al. Differential desensitization of homozygous haplotypes of the beta2-adrenergic receptor in lymphocytes. Am J Respir Crit Care Med 2005;172:322–8 (Epub 2005 May 5).
216. de Coupade C, Gear RW, Dazin PF, et al. Beta 2-adrenergic receptor regulation of human neutrophil function is sexually dimorphic. Br J Pharmacol 2004;143:1033–41 (Epub 2004 Oct 11).
217. Bernardin G, Strosberg AD, Bernard A, et al. Beta-adrenergic receptor-dependent and -independent stimulation of adenylate cyclase is impaired during severe sepsis in humans. Intensive Care Med 1998;24:1315–22.
218. Hoen S, Mazoit JX, Asehnoune K, et al. Hydrocortisone increases the sensitivity to alpha1-adrenoceptor stimulation in humans following hemorrhagic shock. Crit Care Med 2005;33:2737–43.
219. Kobayashi Y, Muldoon SM, Kiyose M, et al. Inhibition by midazolam of the adrenergic function in the isolated canine mesenteric vein. Acta Anaesthesiol Scand 1998;42:1157–63.
220. Waugh DJ, Gaivin RJ, Damron DS, et al. Binding, partial agonism, and potentiation of alpha(1)-adrenergic receptor function by benzodiazepines: a potential site of allosteric modulation. J Pharmacol Exp Ther 1999;291:1164–71.
221. Tsai CS, Hsu PC, Huang GS, et al. Midazolam attenuates adenosine diphosphate-induced P-selectin expression and platelet-leucocyte aggregation. Eur J Anaesthesiol 2004;21:871–6.
222. Hsiao G, Shen MY, Chou DS, et al. Mechanisms of antiplatelet and antithrombotic activity of midazolam in in vitro and in vivo studies. Eur J Pharmacol 2004;487:159–66.
223. Goto Y, O'Malley C, Fanning NF, et al. Benzodiazepines inhibit the rate of neutrophil apoptosis. Ir J Med Sci 2003;172:191–4.
224. Krumholz W, Reussner D, Hempelmann G. The influence of several intravenous anaesthetics on the chemotaxis of human monocytes in vitro. Eur J Anaesthesiol 1999;16:547–9.

225. Locker GJ, Mader RM, Rizovski B, et al. Negative chronotropic effects of fentanyl attenuate beneficial effects of dobutamine on oxygen metabolism: hemodynamic and pharmacokinetic interactions. J Pharmacol Exp Ther 1999;290(1):43–50.
226. Garrido E, Perez-Garcia C, Alguacil LF, et al. The alpha2-adrenoceptor antagonist yohimbine reduces glial fibrillary acidic protein upregulation induced by chronic morphine administration. Neurosci Lett 2005;383:141–4.
227. Ohara T, Itoh T, Takahashi M. Immunosuppression by morphine-induced lymphocyte apoptosis: is it a real issue? Anesth Analg 2005;101:1117–22, table of contents.
228. Ballesta JJ, Orts A. Interaction of opioid drugs with human platelet alpha 2-adrenoceptors. Eur J Pharmacol 19922;227:349–51.
229. Hsiao G, Shen MY, Fang CL, et al. Morphine-potentiated platelet aggregation in in vitro and platelet plug formation in in vivo experiments. J Biomed Sci 2003;10:292–301.
230. Kozek-Langenecker SA. The effects of drugs used in anaesthesia on platelet membrane receptors and on platelet function. Curr Drug Targets 2002;3:247–58.
231. Cammarano WB, Pittet JF, Weitz S, et al. Acute withdrawal syndrome related to the administration of analgesic and sedative medications in adult intensive care unit patients. Crit Care Med 1998;26:676–84.
232. Laorden ML, Fuertes G, Gonzalez-Cuello A, et al. Changes in catecholaminergic pathways innervating paraventricular nucleus and pituitary-adrenal axis response during morphine dependence: implication of alpha(1)- and alpha(2)-adrenoceptors. J Pharmacol Exp Ther 2000;293:578–84.
233. Streel E, Dan B, Campanella S, et al. A pharmacological modulation of opiate withdrawal using an up-/down-regulation of the noradrenergic system in opiate-dependent rats. Int J Neuropsychopharmacol 2005:1–6 (Epub ahead of print).
234. Nakai T, Hayashi M, Ichihara K, et al. Noradrenaline release in rat locus coeruleus is regulated by both opioid and alpha(2)-adrenoceptors. Pharmacol Res 2002;45:407–12.
235. Bruder N, Lassegue D, Pelissier D, et al. Energy expenditure and withdrawal of sedation in severely head-injured patients. Crit Care Med 1994;22:1114–9.

Address for Correspondence
John F. Stover, MD
Departement Chirurgie
Chirurgische Intensivmedizin
Universitäts Spital Zürich
Rämistrasse 100
8006 Zürich
Switzerland
e-mail: john.stover@usz.ch