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Traumatic brain injury-induced autoregulatory dysfunction and spreading depression-related neurovascular uncoupling: pathomechanisms, perspectives and therapeutic implications

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Abstract

Traumatic brain injury (TBI) is a major health problem worldwide. In addition to its high mortality (35-40%) survivors are left with cognitive, behavioral and communicative disabilities. While little can be done to reverse initial, primary brain damage caused by trauma, the secondary injury of cerebral tissue due to cerebromicrovascular alterations and dysregulation of cerebral blood flow (CBF) is potentially preventable. This review focuses on functional, cellular and molecular changes of autoregulatory function of CBF (with special focus on cerebrovascular myogenic response) that occur in cerebral circulation after TBI and explores the links between autoregulatory dysfunction, impaired myogenic response, microvascular impairment and the development of secondary brain damage. We further provide a synthesized translational view of molecular and cellular mechanisms involved in cortical spreading depolarization-related neurovascular dysfunction, which could be targeted for the prevention or amelioration of TBI-induced secondary brain damage.

Keywords: autoregulation, neurovascular coupling, brain damage, myogenic, spreading depression

1. Introduction

Traumatic brain injury (TBI) occurs when the head is hit directly or indirectly by an object (e.g. during a fall or a traffic accident) or by blast waves, or when an object (e.g. a projectile) pierces the skull and enters the brain parenchyma. Each year approximately 1.7 million people in the United States (81, 123, 136) and another 2.5 million patients in the European Union (136) suffer TBI. In addition to a high mortality rate (35-40%) survivors of severe TBI and patients suffering mild but repetitive trauma are left with significant cognitive, behavioral and communicative disabilities imparting an even larger burden to the health care systems (123) and the families of these victims. Epidemiological studies show that approximately 5.3 million people live with TBI-related disabilities in the US (81) and 7.7 million in the EU.(136) Pediatric and elderly populations are the most vulnerable, and specific subpopulations (military workers, athletes, such as boxers, football and hockey players, jumpers, skaters e.g.) are frequently exposed to repetitive head trauma.(24) TBI can be mild, moderate or severe defined by clinical appearance (decrease or loss of consciousness, loss of memory before or after an event, neurologic deficit, alteration in mental state at the time of the injury), imaging findings and various biomarkers. (99)

While little can be done to reverse the initial, primary brain damage caused by trauma, the secondary brain injury (in part) due to vascular/microvascular alterations and dysregulation of cerebral blood flow (CBF) initiated by TBI is potentially preventable. TBI affects practically all tissue and cell types directly or indirectly involved in the regulation of CBF (endothelial cells, astrocytes, pericytes, the blood-brain barrier (BBB), structure of the vascular wall and perivascular innervation, onset of microhemorrhages etc.) leading to traumatic cerebrovascular injury (TCVI).(73, 76) A detailed description of these divergent cerebrovascular consequences of TBI is beyond the scope of the present discussion. In this review the effect of TBI is considered for two unique mechanisms of regulation of CBF: 1) autoregulation of cerebral blood flow and 2) neurovascular coupling in terms of potential mechanisms and pathophysiological consequences. The possible benefits of emerging therapeutic strategies that have the potential to restore vascular and microvascular function and prevent secondary brain ischemia are also briefly discussed.

2. Impaired autoregulation of cerebral blood flow (CBF) after traumatic brain injury (TBI)

Autoregulation of CBF and pathophysiological consequences of autoregulatory dysfunction

The regulation of cerebral circulation has to comply with special requirements. First, cerebral tissue is very sensitive to hypoxia/ischemia, and therefore requires a stable and continuous supply of nutrients and oxygen for normal neuronal function. Second, because the brain is enclosed in the cranium, uncontrolled vasodilation/engorgement would lead to pressure and volume overload of the circulation and an increases in intracranial pressure (ICP). Among others, the two main regulatory mechanisms responsible for meeting these requirements are: 1) pressure-induced vasomotor autoregulation preventing free transmission of changes in systemic blood pressure to changes in CBF and 2) neurovascular coupling adjusting CBF to the metabolic needs of active neuronal/glial tissues.

CBF has to be relatively constant to provide a continuous and stable blood flow to brain tissue despite changes in systemic blood pressure and thus cerebral perfusion pressure (CPP; equal to systemic blood pressure minus ICP), yet allowing heterogeneity in CBF distribution and local functional hyperemia according to the increased neural/glial function. The mechanism fulfilling these requirements is called autoregulation of CBF. Autoregulation of CBF is the integration of myogenic (pressure-induced), metabolic and sympathetic mechanisms (details provided later in the review). (78, 82) These mechanisms adjust the diameter of cerebral resistance vessels and thus cerebrovascular resistance (CVR) to the changes of perfusion pressure: they increase CVR in case of increasing perfusion pressure and

decrease it when blood pressure drops. In other words, cerebral autoregulation is a negative feedback process maintaining stable and constant blood flow when perfusion pressure changes: 1) in hypotension an intact autoregulation prevents hypoperfusion and ischemia of cerebral tissue; 2) in hypertension it protects the cerebral microvascular bed against hyperemia and hypervolemia. Mechanisms of CBF autoregulation include static and dynamic components. Static autoregulation of CBF adjusts vascular resistance (thus blood flow) to a steady state perfusion pressure value and it dictates how large changes in perfusion pressure can be compensated. Dynamic cerebral autoregulation restores CBF after rapid, transient changes in perfusion pressure and thus determines how fast the autoregulatory compensation can be implemented. Dynamic and static cerebral autoregulation act on a continuum to maintain CBF when blood pressure changes. Regarding methods to measure autoregulation we refer to other detailed reviews and classical studies of the field. (1, 83-85, 113, 129, 143, 151)

As mentioned above, when autoregulatory mechanisms, due to their impaired capacity to decrease cerebrovascular resistance, cannot maintain approximately unchanged cerebral perfusion when blood pressure decreases, then autoregulatory dysfunction leads to ischemia of cerebral tissue. On the contrary, at high pressure values the significance of autoregulatory mechanisms responsible for maintaining constant blood flow can be appreciated when taking into account the anatomical fact that the brain is situated in the closed cranium consisting of three main volume compartments: cerebral tissue, cerebrospinal fluid and intravascular blood. Volume expansion of one of the compartments can only be compensated by a decrease in the others, as stated in the Kellie-Monroe doctrine and its modified versions.(101) Thus, in case of low intracranial compliance (when compensatory capacity of CSF dynamics is attenuated) an uncontrolled increase in cerebral blood volume (which is the only compartment with higher pressure than normal or even pathological ICP) would lead to sudden increases in ICP and may damage the cerebral microcirculation.(25, 26) This pathophysiological mechanism can be observed for example in hypertensive encephalopathy (116) and in aged mice not able to adapt to hypertension (140, 141). A similar pathophysiological role of autoregulatory dysfunction and consequent vascular engorgement after TBI in the development of edema formation and elevation of ICP is a matter of ongoing debate. In case of brain trauma, theoretically, ICP can be increased either by edema of cerebral tissue or by enhanced cerebrovascular volume (CBV).

Cerebral edema is classified to be either vasogenic or cytotoxic. In case of vasogenic edema (mostly due to blood-brain barrier (BBB) disruption) interstitial fluid accumulates after extravasation. Cytotoxic edema develops following TBI when the metabolic needs of cerebral tissue and nutrient delivery are not met. This situation is usually caused by neuronal hypermetabolism after TBI together with a permanent drop in basal CBF. (90) Because of the lack of energy in maintaining ionic gradients membrane potential is reduced or lost in neurons, which results in depolarization and activation of voltage gated Ca2+ channels. This then leads to glutamate release and subsequent Ca2+ influx, which will result in potassium efflux from neurons and entering of Na+ and Cl- together with water. (50)

The pioneering work of Marmarou *et al*. showed that in patients after severe TBI 1) increased water content of the brain is responsible for increased ICP rather than increased CBV (91), 2) and the increased cerebral water is primarily due to cytotoxic edema and only in part to vasogenic edema.(92) They also demonstrated that CBV decreased after TBI. However, 1) they studied the patients a few hours after the injury, so it is not clear whether or not autoregulatory dysfunction and consequent hypervolemia contributes to the rise in ICP acutely, right after trauma. 2) It is also possible that once cytotoxic edema is developed low CBV is a consequence of the space occupying effect of intracellular water (especially when blood pressure is in the normal range). From this point of view autoregulatory dysfunction and "vasoparalysis" can be a compensatory mechanism to preserve normal ICP. 3) It is also not known what occurs in case of severely elevated systemic blood pressure, when autoregulation should prevent high pressure and volume reaching the brain. Theoretically, in this case, uncontrolled increase in CBV should

further enhance cytotoxic edema-induced high ICP. 4) Finally, lack of autoregulatory protection would lead to increased wall tension when blood pressure increases, which has been shown to exacerbate vascular oxidative stress in cerebral arteries.(130) Cerebrovascular oxidative stress impairs key mechanisms of regulation of CBF, such as endothelial function and neurovascular coupling.(139) The importance of this possibility is underlined by our recent study showing that neurovascular uncoupling alone, without any other circulatory or neuronal changes, is capable to cause cognitive deficit in mice.(137) Neurovascular dysfunction is also considered to be a central mechanism of cognitive decline and dementia due to hypertension, aging, and even Alzheimer's disease. (43, 114)

TBI-induced autoregulatory dysfunction in humans

Clinical studies provide ample evidence that both severe and mild TBI impairs static and dynamic autoregulation of CBF in response to both decreasing and increasing perfusion pressure in adults as well as in children. (23, 25, 26, 38, 39, 75, 103, 104, 107, 111) In the late 1990's (25) and around the year 2000 Czosnyka *et al.* provided further important evidence of disturbed cerebral autoregulation following TBI.(25, 26) Using a dynamic approach they correlated blood flow velocity changes in middle cerebral arteries (MCAs) of patients with spontaneous slow fluctuations in CPP generating a correlation coefficient (Mx) indicative of autoregulatory function: positive values of Mx indicate a correlation between perfusion pressure and blood flow velocity showing passive dependence of CBF on CPP and therefore impaired autoregulation. Similarly, a moving correlation coefficient between spontaneous fluctuations in arterial blood pressure and intracranial pressure can be generated (pressure reactivity index, PRx), which indicates intact autoregulatory function when negative or zero values are shown (blood pressure fluctuations are not transmitted to fluctuations in ICP). (20) Since transmission of blood pressure to changes in ICP are determined by the changes of CVR evoked by changes in intraluminal pressure, PRx is a useful clinical measure to observe and describe pressure-induced myogenic responses of the cerebrovasculature. PRx and Mx correlate with each other being two distinct measures of the same mechanisms. In these studies the averaged flow velocities over perfusion pressure values converged to the shape of the known autoregulatory curve with the lower limit being CPP< 55 mm Hg and upper limit CPP >105 mm Hg. In other words, the upper limit of autoregulation in TBI patients is lower than the physiological value (~150 mmHg). They also found that autoregulation was disturbed in patients with high ICP (>25 mmHg) and low arterial pressure (<75 mmHg). Although increased Mx, PRx and ICP were associated with "unfavorable" outcomes (moderate disability), from these results it is not clear if disturbed autoregulation plays a causal role in the rise of ICP or vice versa. In addition, linking autoregulatory function to secondary injury PRx distinguished between fatal and nonfatal outcomes.

It is very important to note that the onset of autoregulatory dysfunction after TBI is not mandatory, autoregulatory function can be intact following TBI (about 50-90% of severe TBI patients have diminished or absent autoregulatory function).(80, 117, 144) As described above, in autoregulatory dysfunction an optimal value of perfusion pressure can be defined, at which autoregulation functions. Further studies should place a greater emphasis in establishing and understanding the underlying mechanisms of this heterogeneity.

As mentioned above autoregulatory dysfunction can also be caused by mild TBI.(144) Its importance might be best appreciated in chronic, repetitive mild brain trauma, which has been demonstrated to lead to the development of chronic traumatic encephalopathy (CTE) characterized by cognitive and psychiatric problems. The histological hallmark of the disease is the perivascular aggregation of the tau protein with prominent perivascular spaces. (15, 97) In addition to chronic traumatic cerebrovascular injury (amongst others the phenotypic changes of the BBB including the increase of perivascular matrix proteins fibronetctin and perlecan and accumulation of amyloid β due to disturbed perivascular drainage).(72-74)

In addition to the mentioned mechanisms Bailey *et al.* provided important evidence that autoregulatory dysfunction is also involved in the pathology of CTE. They found that dynamic autoregulation of CBF is impaired in professional male boxers compared to age- and physical-fitness-matched male non-boxers, which was associated with fronto-temporal neurocognitive dysfunction and the volume and intensity of sparring, during which most of the mild head trauma occurred. They also demonstrated a more marked orthostatic hypotension in boxers, which can lead to transient cerebral hypoperfusion due to the lack of autoregulatory compensation. (14) Autoregulatory dysfunction may also participate in the development of post-concussive symptoms after non-repetitive mild TBI in the pediatric population.(15)

Autoregulatory dysfunction in animal models of TBI

Experimental studies provided further evidence for TBI-induced autoregulatory dysfunction, corroborating the clinical findings. Lewelt *et al.*(88) applied low (1.5 to 2.2 atmospheres) and severe (2.8 to 4.8 atmospheres) fluid percussion injuries on cats, and measuring CBF after impact using the hydrogen clearance technique in response to decreasing blood pressure achieved by bleeding of the animals. They observed intact autoregulatory responses in 3 out of 8 cats in the low-pressure trauma group. In the severe group 3 out of 8 cats had no autoregulatory function: CBF decreased as a function of blood pressure. Two animals maintained CBF until 100 mmHg and the remaining maintained CBF until 80 mmHg indicating impaired but partly preserved autoregulatory function (heterogeneity of autoregulatory dysfunction after TBI). DeWitt *et al.* also confirmed these findings in cats.(30) Similar results were obtained in rats (40) using laser Doppler flowmetry demonstrating impaired autoregulatory response to bleeding-induced hypotension 24 hours after impact-acceleration injury.

A rat study from the Povlishock laboratory observing direct arteriolar dilation also showed that the autoregulatory response to reduction in blood pressure is impaired after impact acceleration and lateral fluid percussion injuries. (48) Extending these findings, Nawashiro *et al.* showed that impact acceleration injury also disrupts autoregulatory function in response to increases in blood pressure. (106) On the contrary, however, Bedell *et al.* reported (16) that CBF response to hypotension after a parasagittal fluid percussion injury in Sprague-Dawley rats does not change and is not affected by hypothermia. Although the presented data show no significant difference between the groups, the mean arterial pressure-CBF curve of the injured rats trended toward a steeper curve than control rats, and the use of isoflurane anesthesia (known to dilate cerebral vessels) may have influenced the results.

In summary, human and experimental studies provided evidence that TBI heterogeneously impairs autoregulation of CBF, which is associated with both unfavorable and fatal outcomes.(20, 25, 26, 71) Dysfunctional autoregulation has bidirectional consequences: it results in ischemia with relatively small reductions in blood pressure (thus increasing cytotoxic oedema), and permits marked increases in CBF with modest increases in blood pressure. Although cytotoxic edema seems to be the primary factor in TBI-related development of cerebral edema formation and in the increases of ICP, autoregulatory dysfunction-related increase in CBV may increase microvascular volume and exacerbate extravasation when the BBB is disrupted (BBB disruption is most likely permissive for the development of autoregulatory dysfunction-related oedema formation, because an intact BBB is capable of preventing the extravasation of intraluminal fluid by active osmotic compensatory mechanisms even during severely increased hydrostatic pressure in the arteriolar and capillary bed).(54) It is also possible that a bidirectional pathological link may exist: autoregulatory dysfunction likely promotes pressure-induced injury to the microvascular endothelial cells, leading to disruption of the BBB (140). This concept is supported by the findings that mannitol is less effective in reducing ICP when autoregulation is impaired. (103) Regarding the cellular and molecular mechanisms of TBI-induced microvascular injury and BBB disruption, we refer to other recent reviews.(2, 3) When blood pressure is above the normal range, autoregulatory

dysfunction, by allowing greater blood volume and pressure to enter the brain, may enhance cytotoxic edema-related increased ICP. Pathological consequences of the dysfunction of mechanisms maintaining the upper part of the autoregulatory curve after TBI need further studies both in humans and animal models.

Mechanisms of autoregulatory dysfunction after TBI

Role of impaired pressure-induced myogenic response in autoregulatory dysfunction associated with TBI

The purpose of autoregulation is to adjust CVR in response to changes in perfusion pressure in order to maintain a nearly constant CBF. Cerebral arterial vessels actively dilate and constrict when blood pressure decreases or increases, respectively. This pressure-induced myogenic response plays a central role in CBF autoregulation. (11, 17, 18, 22, 42, 45, 47, 49, 57, 59, 95, 96, 98, 102, 110, 140, 146) Several studies demonstrated that TBI impairs both myogenic dilation and constriction of cerebral resistance vessels. The myogenic function of cerebral vessels can be studied *in vivo* by observing the responses of pial arteries and arterioles through a cranial window in response to changes in blood pressure(48) or *ex vivo* by using pressure myography(138). The latter approach when using isolated vessels has the advantage of primary impairment of pressure-induced intrinsic vascular responses being identified without the confounding effects of factors produced by neurons and glia after TBI.

Previous studies using pressure myography showed that isolated MCA of rats exhibit impaired myogenic dilation in response to decreases in perfusion pressure after severe controlled cortical impact. This observation supports the concept that TBI primarily impairs vasomotor mechanisms intrinsic to the vascular wall. The findings that TBI-induced impairment is present on both the ipsilateral (2 and 24 hours after impact) and the contralateral side (24 hours after the impact) (51) suggest that TBI leads to a generalized vasomotor dysfunction in the cerebral microcirculation. Similarly, decreased myogenic dilation can also be demonstrated in isolated rat MCAs shortly after fluid percussion injury (93).

Recent studies (145) showed that in isolated rat MCAs myogenic constriction is also decreased after moderate fluid percussion and severe weight-drop injury. Although the clinical importance of these observations was demonstrated by Budohoski *et al.* showing that negative or zero pressure reactivity index (which is a surrogate of intact cerebrovascular myogenic function (*vide supra*)) correlates with both intact autoregulatory function and better outcome in TBI patients (20), the molecular mechanisms of the TBI-related impairment of cerebral myogenic function are less known.

Cellular mechanisms of impaired myogenic dilation of cerebral vessels after TBI

The mechanisms of impaired myogenic dilation of cerebral vessels after TBI are likely multifaceted. TBI induces excessive production of vascular nitric oxide (NO)(126, 145) and accumulation of (in part NADPH oxidase-derived) reactive oxygen species, such as O2-.(77). These processes together lead to the production of peroxynitrite (ONOO-).(29) In both endothelial and smooth muscle cells, peroxynitrite was shown to inhibit vascular Ca2+-activated K+ channels(19), thus causing constriction of cerebral arteries.(37) Since BK channels were demonstrated to contribute to myogenic dilation (13), this mechanism is likely to be involved in TBI-related impairment of myogenic dilation. An interesting study from the DeWitt laboratory showed that scavenging TBI-induced production of ONOO- restores myogenic dilation of rat MCAs via improving gap junction communication between smooth muscle cells.(150) Prostaglandins, especially PGE2, have been demonstrated to contribute to dilation of pial arteries in response to hypotension, which is disturbed by fluid-percussion injury in newborn pigs.(7) However, findings of Dabertrand *et al.* make these results controversial providing substantial evidence that isolated cerebral arterioles of rats and mice constrict, rather than dilate to

PGE2 administration. (27) It has to be noted that responses of human cerebral arterioles to PGE2 administration are not known.

Another interesting possibility is the role of TBI-induced production of tissue plasminogen activator (tPA). Armstead *et al.* showed that in a newborn pig an inactive tPA variant (tPA-S481A) prevents the impairment of autoregulation when administered 30 minutes after fluid percussion injury (FPI) by inhibiting over-activation of N-methyl-D-aspartate (NMDA) receptors. TBI results in increased production of the vasoconstrictor endothelin-1 (ET-1), and tPA-S481A also inhibits the endothelin-1 receptor.(8) In addition, ET-1 antagonizes NMDA receptor mediated vasodilation(6) and leads to impaired dilation of cerebral vessels mediated by K+ channel agonists after FPI, via release of superoxide anion. The role of ROS is also suggested by studies of Kim *et al.* showing that arteriolar dilation to hypotension after FPI was restored by both 1) the transfer of human copper-zinc (Cu/Zn) superoxide dismutase (SOD) into rats via intracisternal administration of recombinant adenoviruses, and 2) treatment of the pial circulation with the NADPH oxidase inhibitor diphenyleneiodonium. (77) On the other hand, ROS production may play a beneficial role in preserving dilator capacity of cerebral vessels: an interesting study of Sullivan *et al.* demonstrated that NADPH oxidase 2 (NOX2)-derived reactive oxygen species activate Ca^{2+}-permeable transient receptor potential ankyrin 1 (TRPA1) channels on the cerebrovascular endothelium leading to Ca^{2+}-influx. These Ca^{2+} ”sparklets” activated intermediate-conductance, Ca^{2+}-sensitive K^+ channels leading to hyperpolarization of vascular smooth muscle and dilation of vessels.(134) Future studies should examine the effects of the pharmacological and/or genetic activation of TRPA1/intermediate-conductance, Ca^{2+}-sensitive K^+ channels on cerebrovascular tone following TBI.

Cellular mechanisms of impaired myogenic constriction of cerebral vessels after TBI

The vascular processes leading to the impairment of myogenic constriction of cerebral vessels following brain trauma are less understood. As mentioned above, TBI induces excessive production of NO both in cerebral/glial tissue and in the cerebrovasculature. (126, 145) NO was shown to contribute to the initial increase in CBF 30 minutes after trauma (126), and inhibition of NO with VAS203 decreased ICP in mice. (125) Based on these initial findings Villalba *et al.* (145) tested the hypothesis that increased vascular NO is responsible for the absence of myogenic constriction of cerebral vessels after TBI. They found that 24 hours after FPI of rats myogenic constrictions were diminished in both the ipsilateral and contralateral MCAs studied in a myograph chamber. The authors also demonstrated that production of NO was greatly increased in both the endothelial and smooth muscle layers of MCAs after TBI, and that inhibition of NO production with L-NNA increased myogenic tone of the impacted vessels.

Along with these functional data they showed that TBI enhanced vascular expression of inducible nitric oxide synthase (iNOS). They also showed that constrictions after inhibition of guanylyl cyclase, protein kinase G (PKG) and BK channels were decreased in animals after trauma. Based on these findings, the authors proposed that TBI triggers endothelial production of iNOS-derived NO, which then decreases pressure-induced smooth muscle Ca2+ concentration due to hyperpolarization after the cGMP (cyclic guanosine monophosphate)/PKG (Protein kinase G)-dependent activation of BK channels. (145) Although the effect of inhibition of NO production on the myogenic response of MCAs is convincing, after the treatment myogenic tone seems to be lower at 80 and 100 Hgmm compared to control vessels, and the pressure range over 100 mmHg is not covered by the study. Thus it is not clear if NO is responsible for the loss of myogenic constriction at higher pressure values and whether NO has a permissive or a direct role in the impairment of the pressure-induced constriction. In other words: is NO produced in response to pressure after TBI?

Although the vascular endothelium is capable modulating vascular myogenic tone (for example flow induced dilation attenuates pressure-induced constriction when flow and pressure change

simultaneously)(142), it is not thought to contribute to myogenic constriction, and this would support a permissive role (for a review on the topic please see (28). The vessels did not constrict to the thromboxane analogue U46619 or to potassium, as they did in controls, indicating that MCAs lost their ability to constrict to agonists beyond the effect of pressure-induced constriction. This would further support the permissive, indirect role of NO in the defective myogenicity of cerebral vessels after TBI. It also further complicates the notion that after TBI peroxynitrite is formed from NO, which is a known constrictor of cerebral vessels. Downstream signaling from NO in myogenic constriction after TBI is also in question since the authors showed constriction to the inhibitors of the mentioned targets instead of the restoration of the myogenic response in the presence of these drugs.

Neurogenic and metabolic effects on autoregulatory function following TBI

In addition to the pressure-induced myogenic response of cerebral vessels other factors are involved in setting CVR during changes in perfusion pressure. Accordingly, neurogenic (sympathetic) and metabolic factors were suggested to contribute to CBF autoregulation, but their role in TBI-induced autoregulatory dysfunction is less known.(55) In newborn pigs following FPI administration of norepinephrine prevented CBF reductions in response to decreasing blood pressure via the inhibition of mitogen activated protein kinases and probably via increasing perfusion pressure.(10) Another interesting study also from Armstead *et al.* (9) demonstrated that in piglets glucagon treatment (known to decrease neuronal glutamate release after TBI) together with the mentioned inhibition of tissue plasminogen activator fully restored hypotension-induced pial arterial dilation after FPI via decreased ERK MAPK and NMDA and increased PGE2-PGI2 levels. Neuronal metabolism is increased after trauma, and together with the acutely decreased basal blood flow, leads to a mismatch between the increased metabolic demand and nutrient supply.(46) Although the increased lactate levels are capable to modulate cerebrovascular tone and thus autoregulatory function, the consequent direct ischemic insult and cytotoxic edema formation play a more important role in TBI-related brain swelling and ICP increase than vascular engorgement and increase in CBF (see above).(90)

3. Spreading depolarization-induced cerebromicrovascular dysfunction: role in secondary injury in TBI

Characteristics of spreading depolarization events and their role in dysregulation of CBF

There is growing evidence that spreading depolarizations (SD), propagating waves of depolarization across the gray matter, contribute to cerebral microvascular dysfunction and pathogenesis of secondary neuronal injury after TBI. SDs recurrent in injured tissue cause a dramatic disruption of ionic homeostasis (58, 128), dendritic beading and swelling of neurons and astrocytes (119, 120, 131), glucose depletion and accumulation of lactate leading to tissue acidosis (44, 67, 122, 124), the release of glutamate together with related neuronal calcium load (69), and typical changes in local CBF (12). Regarded originally as an experimental curiosity, spontaneously generating SD has proven to be a potent pathogenic mechanism in neurological diseases such as migraine with aura, subarachnoid hemorrhage, ischemic stroke and TBI (32).

It has been recognized that SDs establish the initial damage of the ischemic core as well as secondary lesion growth into the penumbra of focal ischemia. (62) The initial mass tissue depolarization that follows the drop of CBF bellow a critical threshold (5-10 ml/100g/min) with a short delay (i.e. 2-5 min) is a persistent SD, which defines the primary infarction. Subsequently, additional repetitive SDs recur spontaneously for hours or days in the penumbra region(35, 61, 133), where insufficient perfusion sets the scene for a critical supply-demand mismatch to trigger SDs (147). These later SDs propagate slowly (1-8 min/mm) across the cortex and convert electrically silent but viable penumbra tissue into the core

region, thereby expanding the infarcted zone. Recent clinical studies have shown that SD emerges as a potent pathomechanism of the progression of secondary injury in TBI, as well. (63, 65, 68)

The characteristic features of SD are a large, transient negative shift in the slow electrical or direct current (DC) potential and the simultaneous silencing of brain electrical activity termed spreading depression (Fig. 5A). (52, 87) The SD-related negative shift of the DC potential represents the complete loss of resting membrane potential to a near 0 mV reflecting an increase of extracellular K^+ from 3-4 mM to 30-60 mM, and the concomitant decrease of the extracellular concentration of Na^+ from 140-150 mM to 50-70 mM and of Ca^{2+} from 1-1.5 mM to 0.2-0.8 mM (115). At the level of the brain tissue, SD is an intense, self-igniting, local depolarization of a critical mass of cells, which propagates to adjacent cell populations in the cerebral gray matter by means of increasing extracellular K^+ or glutamate concentration. (128)

In the rat, the physiological pattern of SD-associated CBF response includes four sequential components: 1) an initial, brief drop of CBF; 2) a marked, transient peak hyperemia; 3) a less obvious late hyperemia; and 4) a sustained hypoperfusion also known as spreading oligemia. (12) The share of these four elements in the CBF response is variable, with the peak hyperemic element being the most conspicuous. The hyperemic component is comparable to functional hyperemia of physiological neurovascular coupling, as it supplies the brain tissue with energy substrates to be used by ion exchange pumps for the restoration of resting membrane potential. Comprehensive analysis and comparison of the CBF response in the rat and patients revealed a good correspondence. (109) Therefore, data obtained from rat models have an accepted relevance for human disease states.

In the ischemic brain, the CBF response to SD is more dominated by vasoconstrictor mechanisms, and low perfusion pressure further limits the extent of blood flow increase. (44, 70) Thus, hyperemia is diminished while ischemic components are more pronounced. (100, 149) In the most severe form, the vasoconstriction completely overrides dilatation (Fig. 5B) and causes pathologic inverse neurovascular coupling, known as spreading ischemia. (32) This atypical SD-associated CBF variation during ischemia aggravates metabolic supply-demand mismatch in the tissue and can delay recovery from SD. Longer cumulative SD duration, in turn, increases the probability of neuronal cell death and eventually infarction. (31, 32, 35)

The different phases of the SD-related CBF response are assumed to be the result of a sequence and combination of extracellular ionic, neurotransmitter, and metabolic changes. (12) These include, for example, interstitial K^+ elevation, variation in the release of nitric oxide or prostaglandins, or the modulation of adenosine receptors. (12) Because of the complexity of these interactions, it is rather challenging to discriminate the significance of individual factors. Still, it has been suggested that a high level of extracellular K^+ exceeding 20 mM concentration (vasoconstrictor stimulus) in combination with decreased nitric oxide availability (permissive vasodilator agent) promote vasoconstriction, and thereby trigger the shift to spreading ischemia with SD. (33, 148) These conditions are present in TBI, as interstitial K^+ is markedly elevated (118) and the availability of nitric oxide may be limited by fast reaction with superoxide to form reactive nitrogen species (56). In addition, the produced peroxynitrite could promote vasoconstriction by the potential inhibition of vascular Ca^{2+}-activated K^+ channels,(19) as described above. Such pathophysiological conditions may favor the development of spreading ischemia as a consequence of SDs.

Evidence for the occurrence and injurious potential of SD in TBI patients

The confirmation of SD occurrence in patients was delayed for many years by the lack of an appropriate methodology. SD propagation escaped detection on regular scalp EEG possibly because bone and other tissue greatly alter the electrical signal, and the frequency filtering, amplification, and time-scale display of conventional EEG are not optimal to reveal SDs.(36, 66) Thus, the first evidence for SD

to occur in the neocortex after TBI was obtained with invasive probes. Monitoring of extracellular K^+ concentration with a surface minielectrode in the cortex, in combination with the assessment of local CBF and tissue metabolism (tissue NADH levels) revealed recurrent SDs at the sampling site about every 30 min, leading to the recording of more than 40 events in a comatose patient. These SDs appeared as transient increases of interstitial K^+ level, coupled with typical hemodynamic responses resembling those previously seen with SDs in the rodent brain. (94)

A more generalizable/applicable approach to monitoring SD was then developed by adapting electrocorticographic (ECoG) techniques used in epilepsy monitoring to the post-operative monitoring of TBI. SD was originally discovered in rabbits as transient, abrupt reductions in ECoG amplitude acquired by cortical surface electrodes (87) Thus, in a groundbreaking study, Strong and colleagues placed ECoG electrode strips on the cortical surface in patients who required surgery for traumatic intracranial hematoma. This study demonstrated that spreading depression of the ECoG signal occurs commonly in TBI patients. (133) Subsequent studies then showed that the spreading depressions are accompanied by the hallmark negative DC shift of SD.

DC shifts were first revealed as slow potential changes recorded with AC-coupled amplifiers (41), then by reconstruction of full-band, DC-coupled recordings from AC-coupled recordings (63), and finally by DC-coupled electrocorticography (34). Recording the DC shift of SD is recognized now as a required standard for identification of these events, since it not only resolves ambiguous signals, but also reveals a subset of SDs that occur without spreading depression of spontaneous activity.(65) SD without spreading depression occurs when spontaneous activity has already been suppressed by ischemia or prior SDs and is termed isoelectric SD.

Once reliable detection of SD in the injured human brain had been established, subsequent studies aimed to determine the incidence and time course of SDs, and conditions that may favor SD elicitation. (63) These studies showed that 55-60% of surgical TBI patients develop SDs and that SDs often occur in repetitive patterns through at least 7 days post-trauma.(54, 56, 57) Lower levels of cerebral perfusion and high systemic temperature are factors that increase the probability of SD, likely through increased mismatch of energy supply-demand (147), although the vast majority of SDs in TBI occur when systemic variables are in normal ranges. (63) Considering the damaging effects of SD in ischemia, the potential of SD to contribute to secondary injury in TBI patients was assessed. As suspected, SDs with prolonged durations and those occurring in association with isoelectricity or periodic epileptiform discharges in the ECoG were predictive of unfavorable outcomes. (60, 65) Taken together, the clinical data confirmed that recurrent SDs do occur spontaneously in the cortex of TBI patients, and specific patterns of these events are independently associated with worse clinical outcome.

An inadequate SD-associated CBF response can delay repolarization by depriving the tissue at risk of essential nutrients required to restore ionic balance across neuronal cell membranes. (12, 32) This CBF response and the duration of depolarization are critical determinants of the harmful effects of SD, since prolonged depolarization in metabolically compromised tissue results in either infarction or selective neuronal necrosis. (62) In order to evaluate the CBF response to SD in patients with aneurysmal subarachnoid hemorrhage, ECoG electrode strips were also equipped with laser Doppler probes. (34) With this technique, spreading ischemia was commonly observed in the human brain, often reducing CBF to ischemic levels. Thereafter, thermal diffusion probes were used alongside ECoG strips for CBF monitoring in TBI patients and inverse neurovascular coupling was similarly observed. (68) As in rodent models of focal ischemia (127), inverse neurovascular coupling in TBI patients was observed in the vicinity of evolving lesions, occasionally during ongoing ischemic episodes (Fig. 6A), and progressively reduced CBF in a stepwise fashion with each successive SD. (68).

Inverse coupling was additionally confirmed by the assessment of the partial pressure of oxygen in the brain tissue in one patient. The data revealed that the change in local partial pressure of oxygen with

SD transformed from physiological transient hyperoxic response to inverse transient hypoxic response over time.(68) In addition, in this study, the inverse CBF response with SD coincided with the loss of autoregulation as assessed by correlations between CBF and mean arterial pressure (Fig. 6B). (68) Importantly, the loss of autoregulation after TBI, as mentioned above, is considered a risk factor for ischemic damage following TBI. Speculatively, the ischemic damage could result from transformation of hyperemic CBF response to SD to spreading ischemia. The evolving characteristics of SDs and impairment of autoregulation suggest that continuous monitoring of these variables is important for personalized diagnosis and treatment of secondary injury (Fig. 7).

Evidence for the occurrence of SD in experimental models of TBI

SD waves were first demonstrated as a sequel of TBI in a rat model of contusional injury induced by fluid percussion. (135) Although the genesis of SD was not universal (i.e. SDs were shown in 6 of the 10 animals), the events were reliably detected as recurrent, transient negative shifts of the DC potential with the concomitant depression of the ECoG. As expected for SD waves, the negative DC shifts were also associated with transient increases of the interstitial K^+ concentration. (79) The first SD occurred approximately an hour after impact, and subsequent SDs occurred as often as 9-10 events/hour. (135) The experiments were later extended by the assessment of regional CBF, using ^{14}C-iodoan tipyrine-based autoradiography. (112) The analysis of the autoradiograms indicated local transient hyperemic CBF response to SDs, superimposed on a baseline CBF considerably reduced by the contusion itself. The response was blunted, however, as CBF barely exceeded baseline flow in the hemisphere contralateral to the injury. (112) The above observations established without doubt that SD occurred spontaneously in the cortex after experimental TBI, with features similar to SD events under cerebral ischemia. The conditions leading to SD elicitation were not defined explicitly, but low CBF in association with SD occurrence and high interstitial K^+ level related to the trauma and SDs were reported (108, 112). It was not explicitly tested whether the SDs augmented injury, although inverse CBF responses to SDs were occasionally observed. Furthermore, the frequency and duration of SDs recurrence were associated with the severity of brain injury. (121) Finally, high frequency SD recurrence in combination with ICP higher than 20 mmHg was concluded to demonstrate advancing secondary injury and poor outcome after TBI. (121)

Although contusions are common with impact injuries, other pathologies such as various types of intracranial hematoma also prevail in severe TBI. Subdural hematoma, for instance, is associated with high morbidity and mortality, and causes injury by raising intracranial pressure, compressing the brain, and triggering a continuum of initial and subsequent SDs, as in focal ischemia. (64) SDs were also shown to emerge following intracerebral hemorrhage in a swine model. (105) Finally, hemorrhage in the subarachnoid space, particularly following hemolysis, can induce neural damage by provoking SDs and scavenging nitric oxide, thereby promoting vasoconstrictive spreading ischemia. (33) These findings together suggest that hemorrhagic lesions in combination with contusions may account for the high incidence of SD in patients with severe TBI. (60, 64)

4. Therapeutic possibilities

At present there are no targeted interventions available to restore autoregulatory function or prevent SDs and concomitant CBF changes in humans with TBI. Current therapeutic efforts focus on normalization of systemic hemodynamic parameters known to affect CBF regulation (blood pressure, plasma osmotic pressure, plasma and erythrocyte volumes and PaO2 and PaCO2 using the so called Lund protocol) in order to maintain adequate perfusion of the injured areas.(53)

On the basis of results from recent studies a fairly novel therapeutic approach emerged, namely maintaining the CPP at a level where autoregulatory function is most preserved and therefore optimal for the individual patient (20, 21, 25, 26, 86) When the pressure reactivity index is monitored over a certain

period, it exhibits a U-shaped curve when plotted as a function of CPP. The optimal CPP for the patient is then determined as the value corresponding to the lowest PRx value of the curve. This value can then be targeted in subsequent patient management as a more personalized approach than simply maintaining CPP within the broad range of 60-140 mmHg considered to be normal for an adult population. The optimal CPP can in theory be targeted more narrowly by ICP control and adjusting blood pressure of the patient, thereby optimizing autoregulatory function. One study provided evidence for the efficacy of this approach: smaller differences between optimal CPP and actual CPP values maintained in patients throughout neurointensive monitoring were associated with more favorable outcomes.(20) Actual CPPs that were well below optimal CPPs were associated with higher mortality, and those substantially above optimal CPPs were associated with increased disability. (5, 132)

In animal models, 1 hour post-traumatic hypothermia was shown to improve TBI-related autoregulatory dysfunction in response to sudden hypotension (48), but these promising result could not be translated to clinical settings.(4) As mentioned above, in newborn pigs administration of norepinephrine prevented CBF reductions in response to decreasing blood pressure via the inhibition of mitogen activated protein kinases (and probably via increasing perfusion pressure). (10) Also, in piglets (9) glucagon treatment and inhibition of tissue plasminogen activator fully restored hypotension-induced pial arterial dilation after FPI. Another interesting study demonstrated that carbon-based antioxidant nanovectors (by annihilation of ROS) targeted to P-selectin on injured cultured cerebral endothelial cells decreased generation of superoxide. (89) Further studies should examine the possibility whether *in vivo* treatment with these antioxidant clusters can restore autoregulation of CBF. Also, further studies should examine whether targeting the involved cellular pathways (Figure 3-4) are capable to prevent and/or treat dilatory dysfunction of cerebral vessels during decreases in perfusion pressure. In order to restore autoregulatory responses to increases in perfusion pressure, further studies are needed to determine mechanisms of impaired myogenic constriction of cerebral vessels.

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Figure legends

Figure 1. Scheme illustrating the consequences of autoregulatory dysfunction after traumatic brain injury. When autoregulatory function is intact (green line) despite changes of perfusion pressure (PP: systemic blood pressure minus intracranial pressure) cerebral blood flow (CBF) is maintained at a near constant level. (Please note that the transient drop in basal CBF following TBI is not depicted on the figure.) The proposed model predicts that following traumatic brain injury autoregulation of CBF is compromised, thus CBF passively changes as a function of perfusion pressure. When perfusion pressure decreases, autoregulatory dysfunction results in significant hypoperfusion and cerebral ischemia. In contrast, when perfusion pressure increases, autoregulatory dysfunction results in cerebral hyperperfusion, leading to increased intracranial pressure. These mechanisms lead to the formation of cytotoxic and vasogenic edema. The resulting decline in oxygen and nutrient supply contributes to secondary injury of cerebral tissue, increasing mortality and compromising functional recovery after traumatic brain injury (TBI).

Figure 2. TBI impairs myogenic response of cerebral arteries. Redrawn original recordings of changes of inner diameters of isolated middle cerebral arteries (MCA) from sham operated rats and rats 24 hours after severe TBI (caused by the weight-drop method) using pressure myography.(138) Please note that the MCA develops an active tone in response to increasing perfusion pressure in control animals, and this myogenic response overlaps the range of autoregulation of cerebral blood flow. Myogenic response is absent 24 hours after the animal suffered severe traumatic brain injury. Passive properties of the vessels did not differ between control and TBI-rats.

Figure 3. Proposed mechanisms underlying impaired myogenic autoregulatory protection after traumatic brain injury (TBI): TBI-induced decreased myogenic dilation. TBI impairs the capability of cerebral vessels to dilate (thus to decrease cerebrovascular resistance), when perfusion pressure drops. For detailed description of these pathways we refer to the text. (BK_{Ca}: large conductance, Ca^{2+}-activated potassium channel, COX-2: cyclooxygenase-2, PGE2: prostaglandin E2, NADPH ox.: NADPH oxidase, GJ: gap junction, ONOO-: peroxynitrite, iNOS: inducible nitric oxide synthase, NO: nitric oxide, NMDA: N-methyl-D-aspartate, NMDAr: N-methyl-D-aspartate receptor, ET-1: endothelin-1, ET-1r: endothelin-1 receptor, tPA: tissue plasminogen activator)

Figure 4. Proposed mechanisms underlying impaired myogenic autoregulatory protection after traumatic brain injury (TBI): TBI-induced impaired myogenic constriction. The mechanisms of the dysfunction of pressure-induced constriction are less known. For detailed description of these pathways we refer to the text. (iNOS: inducible nitric oxide synthase, NO: nitric oxide, GTP: guanosine-5'-triphosphate, cGMP: cyclic guanosine monophosphate, PKG: protein kinase G, BK_{Ca}: large conductance, Ca^{2+}-activated potassium channel.)

Figure 5. The spreading depolarization (SD) phenomenon as assessed at a single recording site by direct current (DC) potential recording (black trace) and AC-electrocorticography (grey trace); and two distinct types of associated cerebral blood flow (CBF) response (red trace) acquired by laser Doppler flowmetry. Representative traces are original recordings from the rat brain. SD was elicited by the topical application of high concentration K^+ in the young intact (A) and the old ischemic (B) parietal cortex.

Figure 6. Inverse neurovascular coupling with spreading depolarization in a representative postoperative case of traumatic brain injury. A, Bipolar electrocortigraphic (ECoG) recordings: black traces depict spreading depolarization (0.01 Hz high pass filtering); blue traces in the background represent spreading depression of activity (0.5–50 Hz bandpass filtering). Synchronous changes of regional cerebral blood flow (rCBF), are shown in the red trace. Note that rCBF drops with each subsequent SD, and returns to lower CBF after the passage of each event. Blood pressure (BP) variations are represented by the gold trace. B, Gradual onset of impaired autoregulation during the period of inverse coupling, as demonstrated by the increasing correlation between CBF and BP. Grey shaded area indicates the range of correlation considered to be significant, indicative of impaired autoregulation. C, Brain images show placement of electrode (Day 1 CT, blue arrow) directly adjacent to an intracerebral hematoma where cortical lesions developed (Day 11 MRI). The figure is reproduced from Hinzman *et al.*(68), 2014 with the permission of Oxford University Press (license number 3816350088958)

Figure 7. A subpopulation of SD events that evolve in TBI is attributed high injurious potential. Recurrent spreading depolarization waves occur in 55-60% of TBI patients requiring surgical alleviation of their symptoms. The insufficiency of the CBF response, which may manifest as spreading ischemia hampers repolarization, thereby prolonging SD. Since longer SD duration has been associated with larger injury, this chain of events is thought to contribute to the expansion of secondary damage in TBI.

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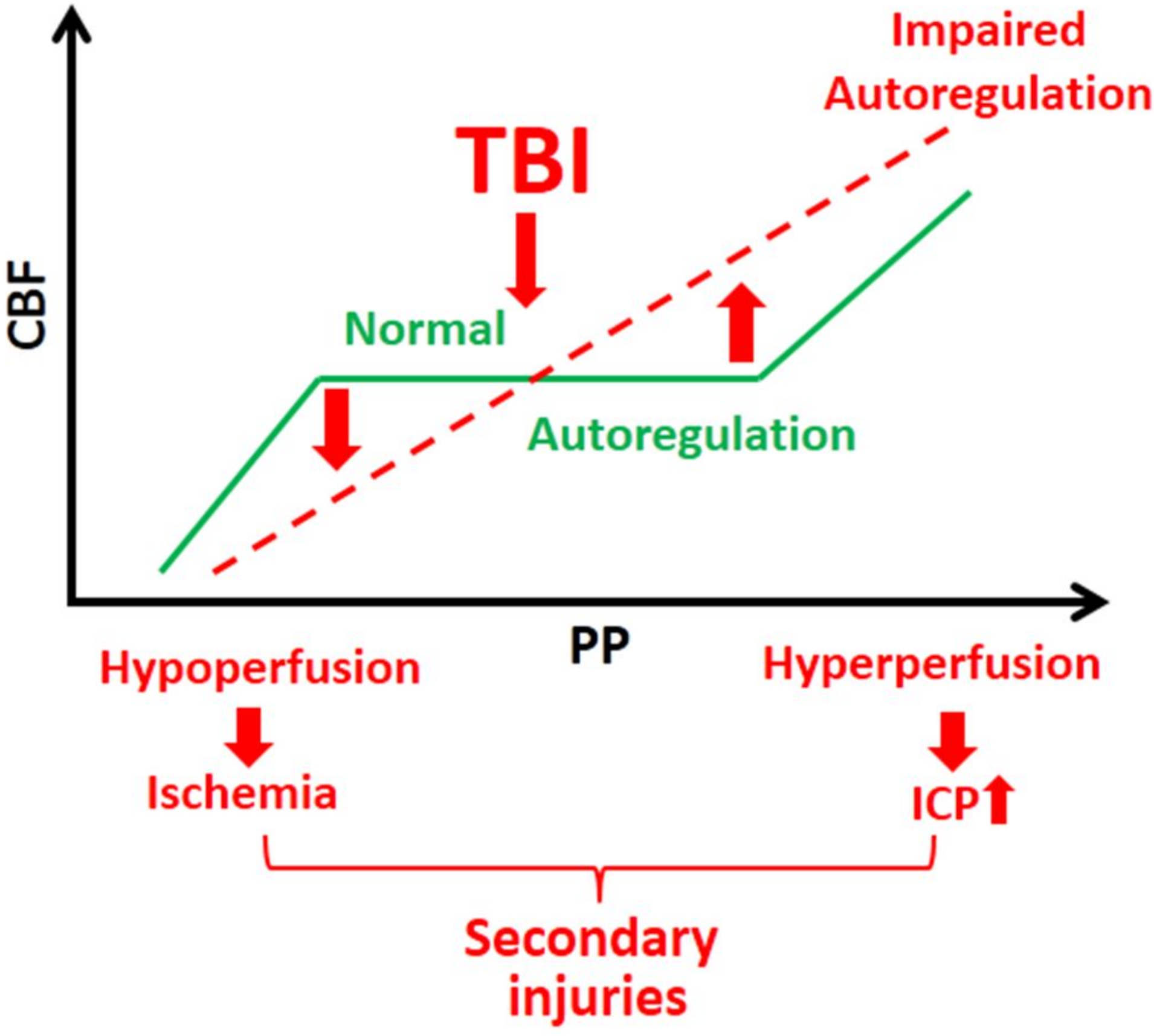
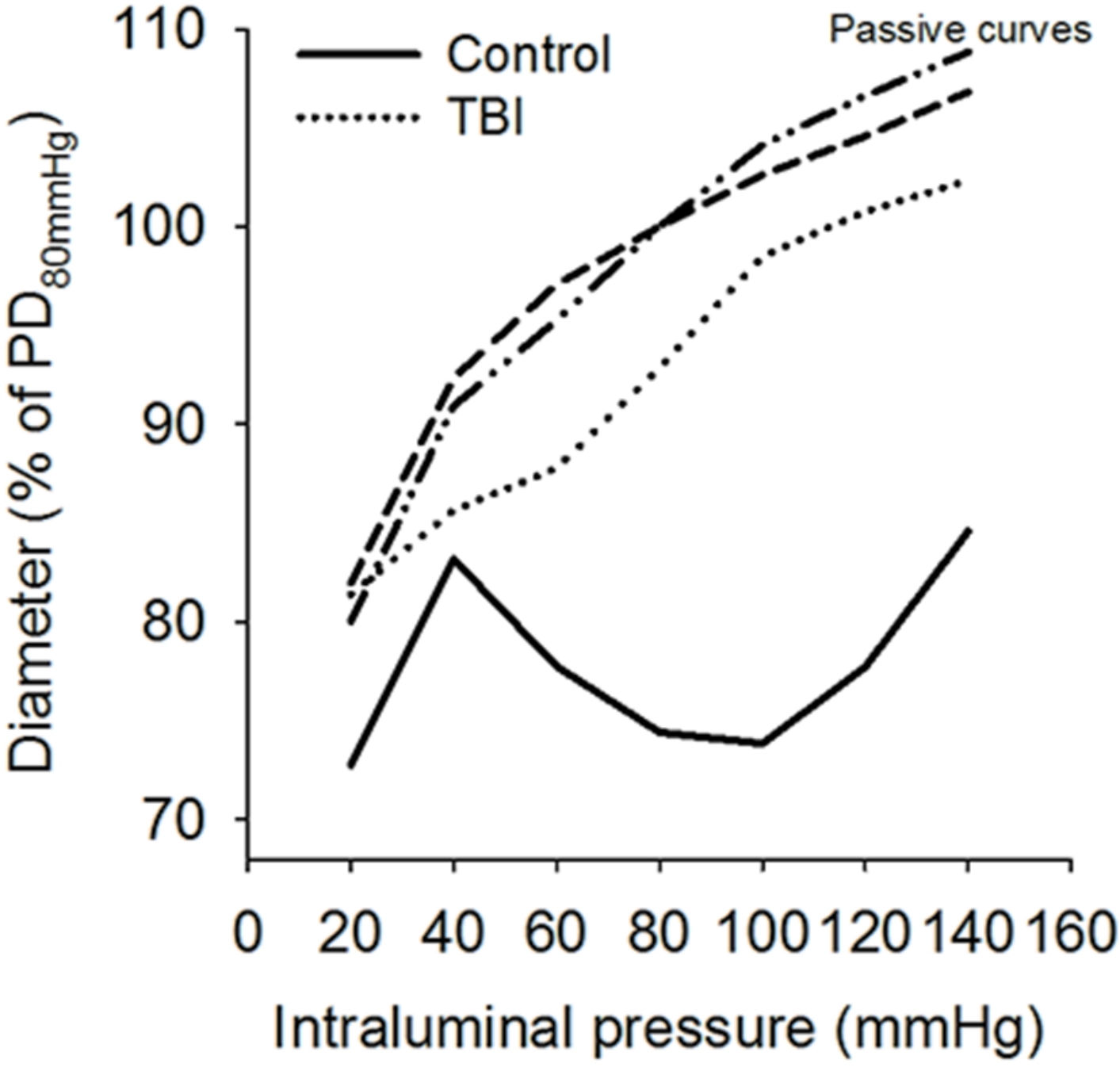

Impaired
Autoregulation
TBI
CBF
Normal
Autoregulation
PP
Hypoperfusion
Hyperperfusion
Ischemia
ICP
Secondary
injuries


Control
TBI
Passive curves
Diameter (% of PD80mmHg)
110
100
90
80
70
0
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40
60
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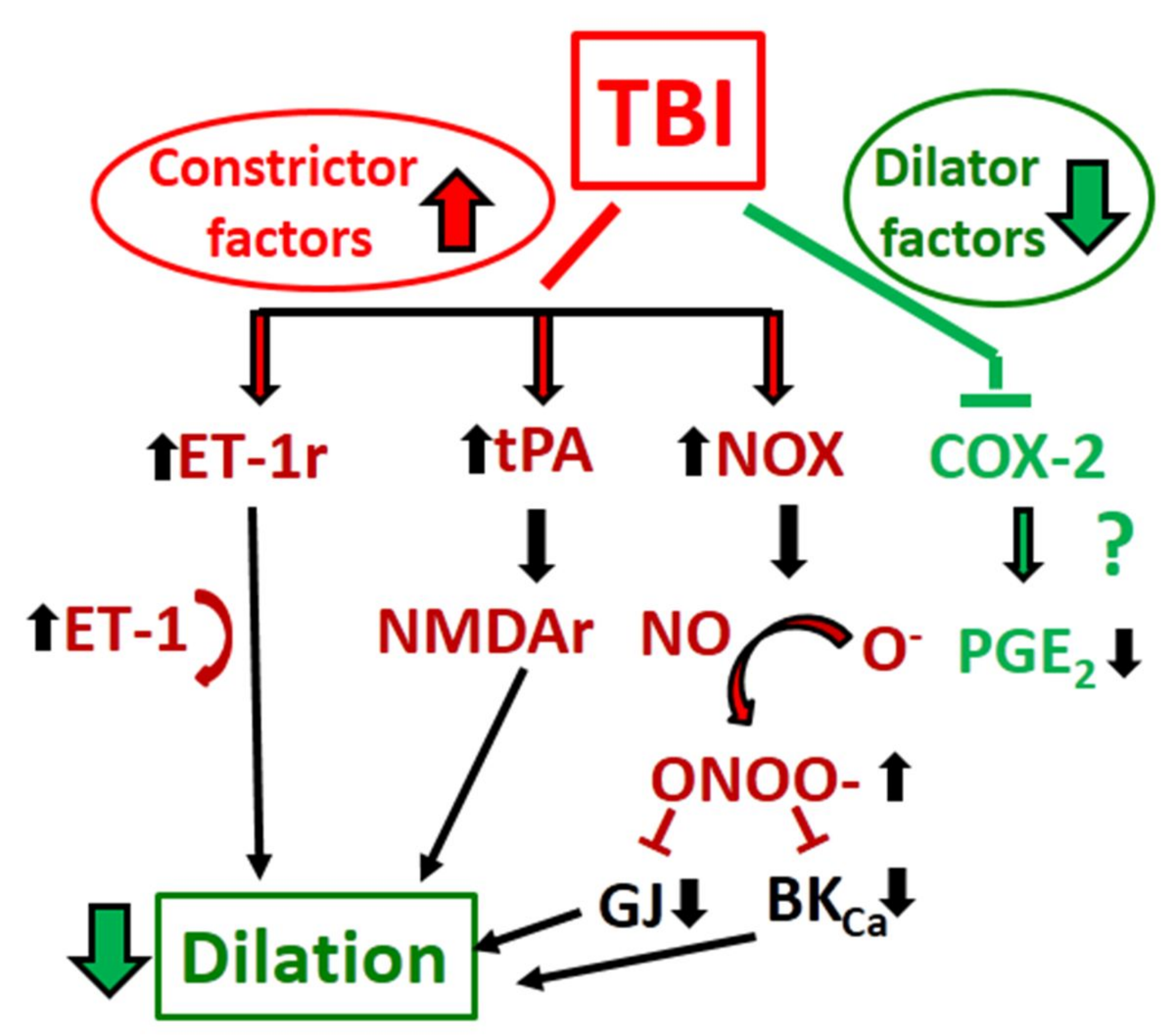
100
120
140
160
Intraluminal pressure (mmHg)


TBI
Constrictor factors
Dilator factors
↑ET-1r
↑tPA
↑NOX
COX-2
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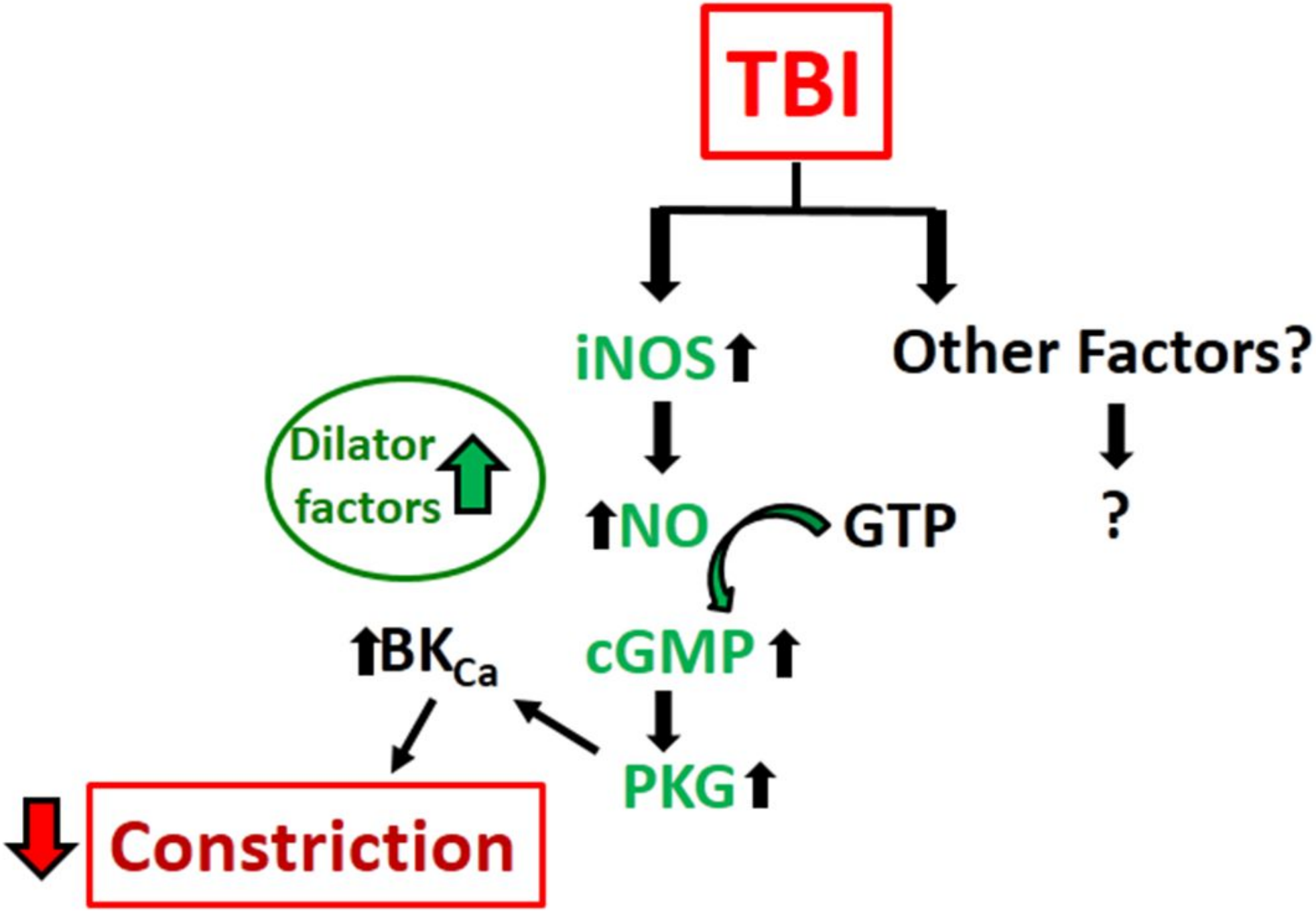
PGE2 ↓
ONOO- ↑
GJ↓
BKCa↓
Dilation


TBI
iNOS
Other Factors?
Dilator factors
NO
GTP
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cGMP
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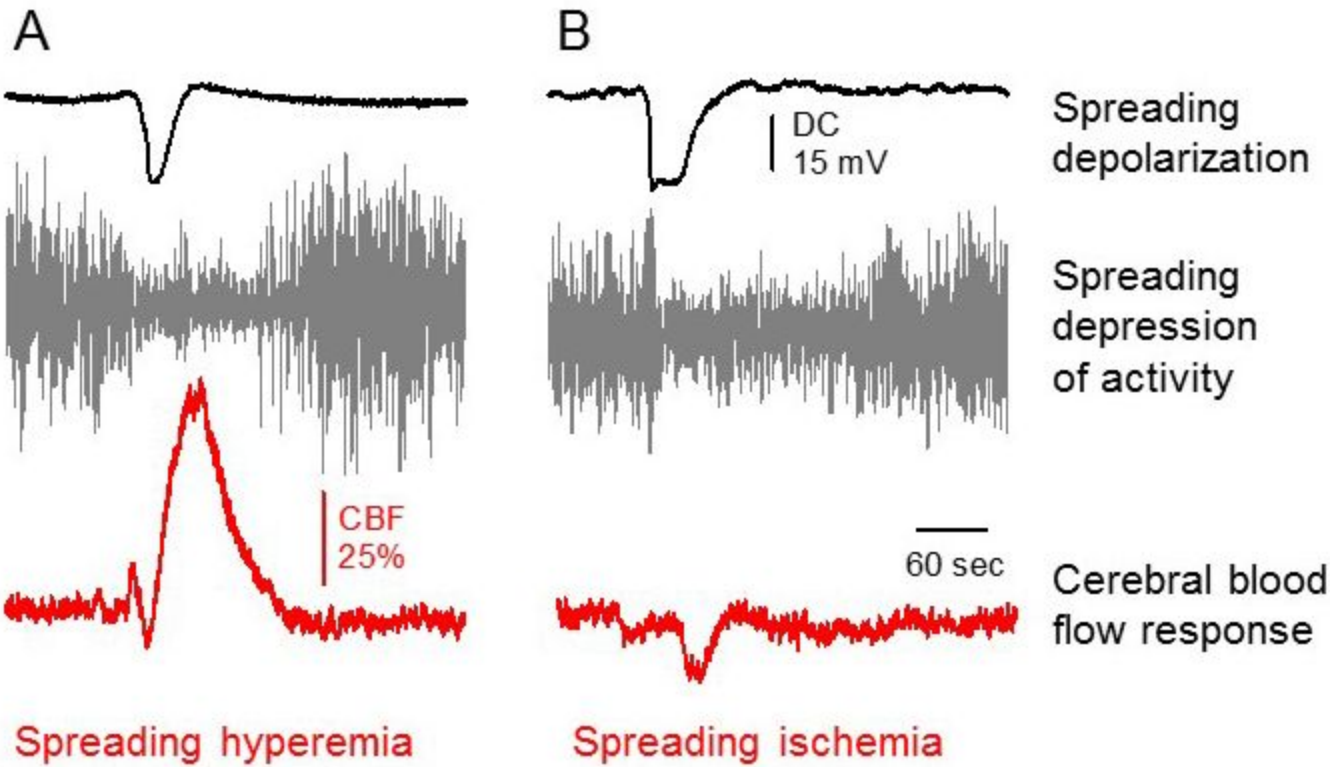
PKG
Constriction


A
B
DC
15 mV
Spreading
depolarization
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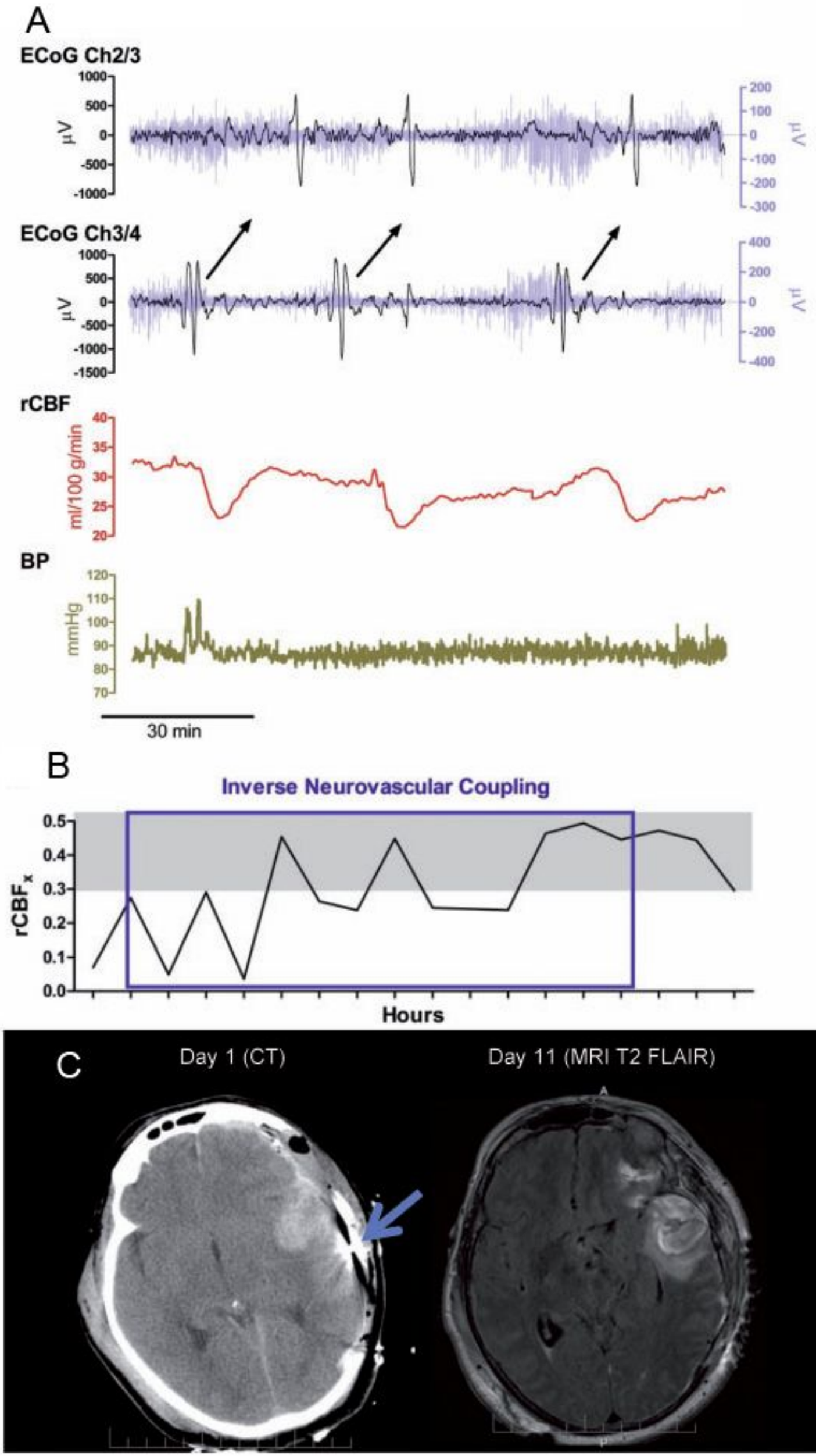
depression
of activity
CBF
25%
60 sec
Cerebral blood
flow response
Spreading hyperemia
Spreading ischemia


A
ECoG Ch2/3
1000
500
0
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-1000
μV
200
100
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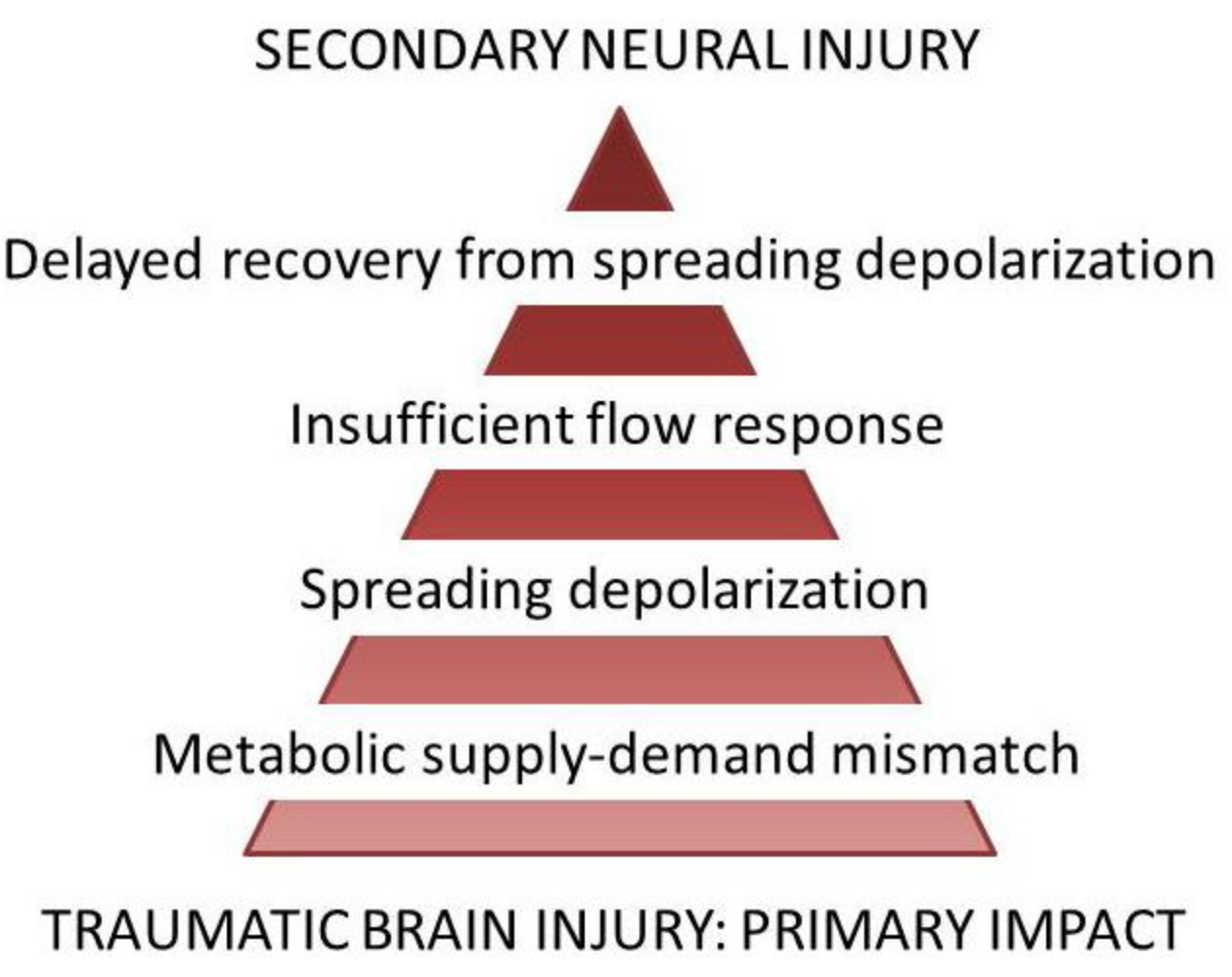
μV
ECoG Ch3/4
1000
500
0
-500
-1000
-1500
μV
400
200
0
-200
-400
μV
rCBF
40
35
30
25
20
ml/100 g/min
BP
120
110
100
90
80
70
mmHg
30 min
B
Inverse Neurovascular Coupling
0.5
0.4
0.3
0.2
0.1
0.0
rCBFx
Hours
C
Day 1 (CT)
Day 11 (MRI T2 FLAIR)


SECONDARY NEURAL INJURY
Delayed recovery from spreading depolarization
Insufficient flow response
Spreading depolarization
Metabolic supply-demand mismatch
TRAUMATIC BRAIN INJURY: PRIMARY IMPACT