Case Report

Indian Journal of Emergency Medicine
Volume 3 Number 1, January - June 2017
DOI: http://dx.doi.org/10.21088/ijem.2395.311X.3117.23

Reperfusion: for Better or for Worse

Ketan Patel[1], Anjali Patel[2], Rignesh Patel[2]

Abstract

Introduction: Cerebral hyperperfusion, or reperfusion syndrome, is a rare, but serious, complication following revascularization. Hyperperfusion is defined as a major increase in ipsilateral cerebral blood flow (CBF) that is well above the metabolic demands of the brain tissue. Quantitatively, hyperperfusion is a 100% or greater increase in CBF compared with baseline. This definition also extends to rapid restoration of normal perfusion pressure, for example, with thrombolytic therapy for acute ischemic stroke. Reperfusion syndrome can occur as a complication of carotid endarterectomy (CEA), intracranial stenting, and even bland cerebral infarction. The prognosis following hemorrhagic transformation is poor. Mortality in such cases is 36-63%, and 80% of survivors have significant morbidity. *Case Report:* A 78 years male hypertensive, diabetic and known coronary artery disease patient came to emergency department with complain of weakness in left upper limb since 4hours which was progressively improving without slurring of speech, leg weakness, palpitation or loss of consciousness. On arrival patient was conscious and oriented with normal vital parameters and normal blood glucose level. On examination patient was having left upper limb power 4/5. Other than that neurological and systemic examination was normal. Patient was undergone basic blood test and Magnetic Resonance Imaging of brain which was suggestive of small acute infarct in right high fronto-parietal region. Patient was treated with dual antiplatelets and supportive measures. On carotid doppler patient was found to have 90% obstruction of internal carotid artery on right side and 60% on left side. Patient was opted for digital subtracted angiography and angioplasty of right internal carotid artery. After the successful completion of procedure patient became progressively drowsy and developed left upper limb and lower limb dense hemiplegia. To rule out intracranial hemorrhage immediately computed tomography of brain was performed and which was suggestive of hyperdense fingerlike projection were noted in sulci all over right side of brain. Differential diagnosis of subarachnoid hemorrhage and hyperperfusion syndrome was suspected. Subsequent computed tomography of brain was suggestive of no hyperdence projections after 24 hours conforming the hyperperfusion syndrome. Patient was treated conservatively and improved in 15 days and discharge home with left hemiparesis. *Disscussion*: An abrupt increase in cerebral blood flow following revascularization has been identified as the direct physiological cause of hyperperfusion syndrome. Several factors including advanced age, underlying leukoaraiosis, and post-procedural high blood pressure have been associated with this condition. Two interlinked and synergistic mechanisms may lead to development of syndrome; impaired cerebral autoregulation and postoperatively elevated systemic blood pressure. If not treated properly, it can result in severe brain oedema, intracerebral hemorrhage, or death. Treatment strategies are directed towards regulation of blood pressure and limitation of rises in cerebral perfusion.

Keywords: Acute Ischemic Stroke; Cerebral Hyperperfusion; Computed Tomography; Hemiplegia.

Author's Affiliation:
[1]Consultant & Head,
[2]Consultant, Dept. of Emergency Medicine, Zydus Hospitals, Ahmedabad, Gujarat 380054.

Corresponding Author:
Ketan Patel, Consultant & Head, Dept. of Emergency Medicine, Zydus Hospitals, Ahmedabad, Gujarat 380054.
E-mail:
drkd25@yahoo.com,
drkd25@gmail.com

Received on 02.05.2017,
Accepted on 16.05.2017

Introduction

In the treatment of acute stroke, restoration of the blood supply can reduce more extensive brain tissue injured by salvaging a reversibly damage penumbra of tissue [1]. This mechanism provides a rationale for clinical trials which have demonstrated that reperfusion after thrombolysis improves clinical outcome in selected patients with acute stroke [2].

Reperfusion, however, carries certain risks. Some patients experience disastrous outcomes in the form of fatal edema or intracranial hemorrhage following thrombolysis [3]. In some animal stroke models [4, 5], reperfusion after a long ischemic period can cause a larger infarct than that associated with permanent vessel occlusion. Thus, while reperfusion may reduce infarct size and improve clinical outcome in some patients, in others it may exacerbate the brain injury and produce a so-called "cerebral reperfusion injury" [4, 6, 7]. Cerebral reperfusion injury can be defined as a deterioration of ischemic but salvageable brain tissue after reperfusion.

Thrombolysis [2] and embolectomy [8, 9] usually result in reperfusion of the infarcted brain tissue and therefore carry the risk of causing reperfusion injury. Thus reperfusion injury deserves the attention of those interested in the diagnosis and treatment of acute stroke. Strategies to reduce or minimize cerebral reperfusion injury require the understanding of the pathophysiology of cerebral reperfusion injury, and the way the reperfusion injury is visualized by magnetic resonance imaging (MRI). Therapeutic options for preventing or attenuating cerebral reperfusion need to be considered.

Cerebral ischemia may be global, affecting numerous vascular territories as in the case of cardiac arrest and cerebral hypoperfusion, or alternatively target a focal region or arterial distribution as in the case of ischemic stroke. The end result in both of these cases is tissue hypoxia, cellular dysfunction and cell death. Circulation in the central nervous system is distinctive due to the fact that large vessels including those of the circle of Willis as well as the extra- and intracranial vessels contribute to approximately half of cerebrovascular resistance [10,11]. Experiencing an episode of prolonged ischemic insult leads to fatal consequences for neurons that extend beyond the failure of cellular energy resources. The cellular changes associated with resultant death include nuclear fragmentation, chromatin condensation and cell body shrinkage [12,13,14]. Changes also occur at the level of the membrane phospholipid structure, which is comprised in part of phosphatidylethanolamine, phosphatidylcholine, phosphatidylserine and sphingomyelin. Studies have proposed a regulatory role for the aforementioned phosphatidy lethanolamine in blebbing and in the formation of apoptotic bodies [15]. This phospholipid also serves a role in mediation of cellular necrosis as its externalization may serve in part to contribute to cytoskeletal organization [15].

Stroke, whether ischemic or hemorrhagic in nature, has the ability to culminate in devastating clinical outcomes. The mechanisms of ischemic stroke are variable, complex and multifactorial in nature. These include thromboembolic stroke secondary to atherosclerosis in the elderly patient population and structural cardiac or vasculopathic / metabolic etiologies in younger patients. Atherosclerosis in itself is one of the most common causes of vascular thrombosis and occlusion and is mediated by atherogenesis. Borderzone infarctions can lead to ischemia in the brain parenchyma, or tissue, by hypoxia to areas in between principal arterial territories. They may occur between the anterior and middle cerebral artery in the case of anterior cortical borderzone infarcts and between the anterior, middle and posterior cerebral territories in the case of posterior borderzone infarctions. Lacunar infarcts, previously thought to result solely from lipohyalinosis, are now thought to ensue from platelet or fibrin clots within an environment of diffuse atherosclerotic small vessel disease [16]. While common causes of embolic stroke include arrhythmias (most prominently atrial fibrillation), structural cardiac pathology such as persistent patent foramen ovale or artery-to-artery thromboembolic phenomenon, another etiology for embolic infarction is septic emboli. These occur typically in the context of systemic infection with seeding of heart valves and more commonly in immunocompromised patients with atypical pathogens including fungal infections and in immunocompetent patients with more common bacterial infections [17]. In these cases, parenchymal damage is mediated by pathogen-mediated inflammation (further contributing to disturbance of the blood / brain barrier, BBB, with cerebral edema), resultant reduction cerebral blood flow and, subsequently, cellular hypoxia and death.

Restoration of vascular supply to an organ temporarily deprived of blood flow, while effective in providing oxygenation, often paradoxically results in injury of the affected tissue bed [18, 19]. This concept has been demonstrated in a variety of organ systems including the brain, heart and kidneys as in the cases

of stroke, myocardial infarction and acute kidney injury, respectively. It has also been seen in the setting of multiorgan ischemia-reperfusion during trauma, cardiac arrest and sleep apnea as well as during surgical procedures including solid organ transplant where acute graft failure and early rejection may be the resultant outcome. Eltzschig and Eckle [19], in 2011, provided a schematic overview of the cellular and molecular mechanisms believed to be involved in reperfusion injury involving both innate and adaptive immune systems as well as the complement system, platelets and coagulation factors. Subsequent to activation of these systems, cell death can occur through a number of mechanisms including both necrosis with a hallmark of cellular swelling and apoptosis involving intricate cell signaling mechanisms for cellular demise [20]. Both processes have been linked to further stimulation of the inflammatory system to include the release of nucleotides acting as signals to promote phagocytosis in the apoptotic tissue bed, leading to more extensive reperfusion injury [18,21]. Additional injury to reperfused tissue has been extensively shown to be mediated by reactive radical oxide species in the brain as well as in other tissues [22-27]. The vascular consequences of injury extend beyond the outcome of cell death to also include a change in the nature of the vascular system as a whole. As a result of the general dysfunction in the cellular metabolic milieu, proinflammatory cytokines lead to endothelial cell inflammation and increased permeability of the vascular system. This injury lasts beyond the period of ischemia, as animal studies have shown the sustained effect of oxidative stress on pericytes in the microvasculature of a middle cerebral artery occlusion murine model, despite arterial recanalization [28].

Case Report

A 78 years male patient came to emergency department with complain of sudden onset of weakness in left upper limb since 4 hours which was progressively improving without slurring of speech, leg weakness, palpitation or loss of consciousness. There was no history of headache, vomiting, shortness of breath, chest pain, abdominal pain, back pain, syncope, vision loss, swallowing difficulty, involuntary movements, and urine or stool incontinence. He was a known case of hypertension since 15 yrs, diabetes type 2 since 10 yrs and coronary artery disease with angioplasty done on left anterior descending artery 8 yrs back. Patient was on regular medicines in form of Tab Amlodepin, Tab Metformin, Tab Ecosprin, Tab Clopidogrel. There was no history of transient ischemic attacks or cerebral vascular accidents.

On arrival patient was conscious and oriented, following verbal commands. Patient was having normal vital parameters inform of Heart Rate- 62/min, Blood pressure- 142/82mmhg, Respiratory rate- 20/min, SpO2- 100% on room air, Temperature- 98.2'F and normal blood glucose level 110 mg/dl. On genreal examination patient was not having any pallor, edema, cyanosis, icterus, clubbing, lymphadenopathy or dehydration. On systemic examination, Neaurolically he was having left upper limb power 4/5. In all other limbs were having power of 5/5. There were no sensory deficits, facial weakness, focal tremors, speech abnormalities or deformity of limbs. Patient was not having any neck rigidity and head jolt test was negative. There were no cerebellar signs as finger to nose test, heel to sheen test and Romberg's test were normal along with no nystagmus and patient was able to walk without any problems. Bilateral pupils were 3 mm bilateral and reacting to light. On respiratory examination patient was having normal bilateral air-entry, with no foreign signs. On cardiovascular examinations, patient was having all peripheral pulses were present and equal, normal heart sounds and no carotid bruits were heard. On abdominal examinations, patient was having soft abdomen with no tenderness and normal bowl sound were present.

Patient was investigated in form of complete blood counts, renal function test, liver enzymes, viral markers, troponin-I, lipid profile, S.homocystien, electrocardiogram, 2D-echocardiograph, carotid Doppler examination and Magnetic Resonance Imaging of brain. All blood reports were normal. Electrocardiograph and 2D-echocardiography were normal. On carotid doppler patient was found to have 90% obstruction of internal carotid artery on right side and 60% on left side.

Magnetic resonance imaging of brain was suggestive of small acute infarct in right high fronto-parietal region, age related changes of atrophy, chronic ischemic changes in periventricular and subcortical white matter. Patient was treated with dual antiplatelets and supportive measures.

Patient was opted for digital subtracted angiography and angioplasty of right internal carotid artery.

After the successful completion of procedure patient became progressively drowsy and developed left upper limb and lower limb dense hemiplegia.

To rule out intracranial hemorrhage immediately computed tomography of brain was performed and which was suggestive of hyperdense fingerlike projection were noted in sulci all over right side of brain.

Differential diagnosis of subarachnoid hemorrhage and hyperperfusion syndrome was suspected. Subsequent computed tomography of brain was suggestive of no hyperdense projections after 24 hours conforming the hyperperfusion syndrome.

Patient was treated conservatively and remained left sided completed hemiplegic which progressively improved over period of 1 month but maximum improvement achieved was only inform of power 2/5 in both upper limbs and lower limbs. This was very important case which was suggestive of harmful effect of reperfusion injury over potential benefits.

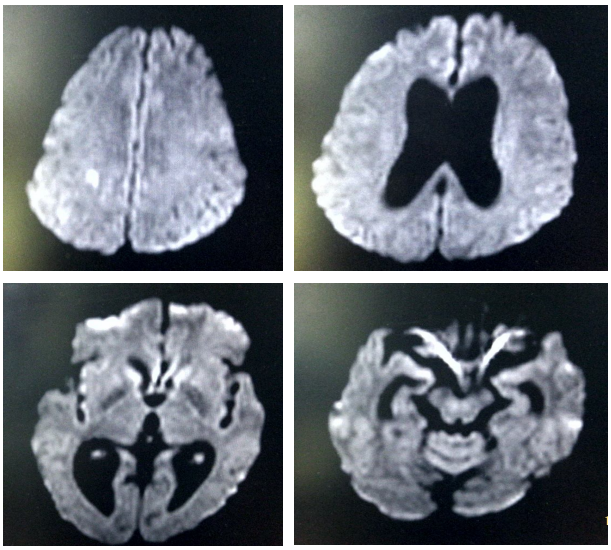


Fig. 1:

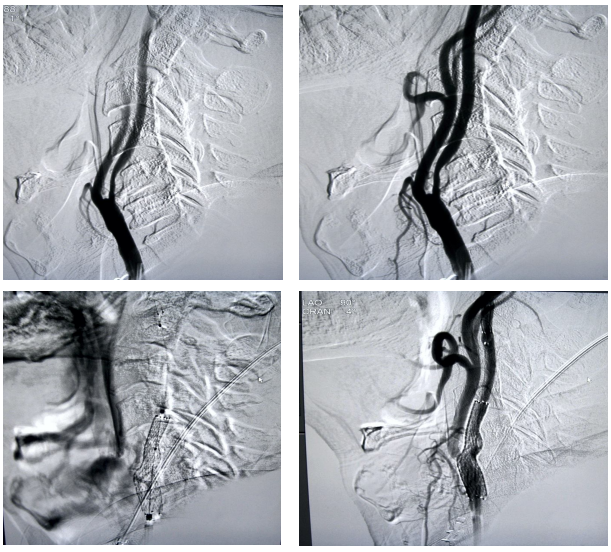


Fig. 2:

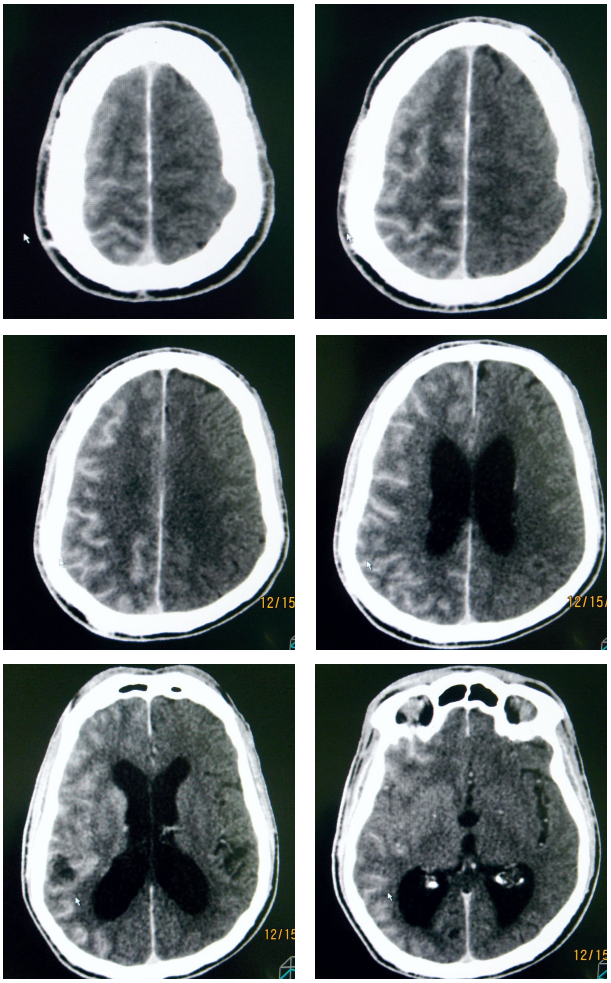


Fig. 3.

Discussion

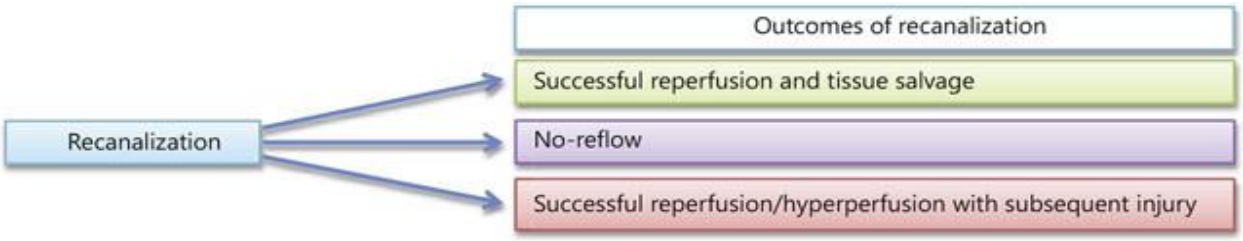
Brain parenchymal damage in the setting of ischemia followed by reperfusion injury (as in other organ systems) occurs as a result of a complex series of events. These events at initiation include an interruption in blood flow to the affected tissue followed by depletion of cellular energy resources and glycolysis at an anaerobic substrate level, subsequently followed by lactic acidosis, failure of sodium potassium pump, release of glutamate, cytotoxic edema, free radical formation and activation of both innate and adaptive immune responses [29,30]. The excessive generation of free radicals overwhelms the system, which then is thought to become inefficient in scavenging these molecules, leading to cellular demise. While ischemic stroke resulting from vascular occlusion by nature limits tissue bed oxygenation, it is believed that cerebral ischemia and hypoxia occur even in the setting of primary hemorrhagic stroke. The mechanism by which this is proposed to occur

happens through a 'multihit theory'. In essence, it is believed that in patients with predisposing factors such as microangiopathy secondary to atherosclerotic disease or amyloid angiopathy, the threshold for tolerance of ischemia is lower and, in the presence of a prothrombotic environment subsequent to hemorrhage, the failure of autoregulation, the increase in intracranial pressure or iatrogenic hypotensive therapy may all act as factors contributing to tissue hypoxia and ischemia [31].

The BBB, due to its unique nature, provides the ability to achieve and maintain cerebral homeostasis. The BBB is constituted by endothelial cells, basement membrane and pericytes, as well as the end feet of astrocytes. Unlike elsewhere in the body, endothelial cells which contribute to the BBB connect via both adherent and tight junctions and lack fenestration. It does, however, afford low permeability due to pinocytic activity [32]. Finally, extracellular matrix proteins contribute to the formation of the basal lamina that connects to endothelial cells by virtue of integrin molecules. Astrocytic end feet help regulate cerebral capillary blood flow, contributing to both the creation and maintenance of the BBB environment [33]. As in the case of reactive oxygen species mediating their long-lasting effects on endothelium and altering the permeability of the vascular system, they are also thought to play a role in altering the permeability of the BBB. Kahles and Brandes [34] review the targets of reperfusion injury on the neurovascular unit, outlining the effects of matrix metalloprotease activation on basal lamina leading to the following: degradation (expression of cell adhesion molecules and stress fiber formation on endothelial cells), followed by contraction (altered expression / distribution / phosphorylation on tight junctions), leading to disassembly and the effect of lipid oxidation (changes in DNA and protein expression in all of the cells of the neurovascular unit) and, finally, oxidative cell damage [34]. Not only can damage related to ischemia-reperfusion occur at the molecular and cellular levels, but a disruption in the BBB contributes to further damage as an increase in vascular permeability causes edema which contributes to impedance in adequate perfusion to the affected tissue bed [35]. In addition to the effects of reactive oxygen species on the neurovascular unit and in altering BBB endothelial cells, excitotoxicity also deleteriously influences astrocyte function, leading in part to inhibition of astrocytic repair as well as end feet detachment, which together disable the BBB. The functional outcome of these events is noted clinically, as studies have shown that the degree of disruption in BBB also correlates with severity of patient outcomes. Using CT perfusion as a reflection of BBB permeability, increased infarct permeability area was proposed as a predictor of poor outcome associated with increased likelihood for undergoing hemicraniectomy in patients with malignant middle cerebral artery infarction [35].

The unique cerebral autoregulatory mechanisms which the brain possesses may also be deleteriously affected as a result of reperfusion injury and result in a loss of adequate control of cerebral blood flow, contributing to further damage [36]. From a purely hemodynamic perspective, cerebral perfusion pressure in an adult with normal blood pressure ranges between 60 and 150 mm Hg [37]. Beyond the lower and upper limits of these ranges cerebral autoregulation is disrupted, resulting in the dependence of cerebral blood flow on mean arterial pressure. Given that vasodilation occurs in the context of cerebral ischemia, reperfusion may lead to hyperemia, which exacerbates neuronal damage by virtue of reperfusion as well as in response to increased perfusion pressures [38].

Hemorrhagic transformation of ischemic infarction is perhaps the most well-recognized consequence of ischemia, followed by reperfusion. The disruption of BBB and subsequent edema, neuroinflammation and continued damage mediated by free radical oxides contribute to the hemorrhagic transformation of ischemic tissue beds following the return of blood flow to the area which once experienced restriction [39]. The concern for this complication, which can lead to worsening of already devastating outcomes of ischemic stroke, influences clinician treatment decisions for aggressive intervention at initial patient presentation. As with the pathophysiology of primary hemorrhagic stroke, subsequent to hemorrhagic transformation, parenchymal injury occurs at multiple levels. It is thought that one of the ways by which this occurs is due to a mechanism akin to traumatic brain injury, given increased pressure and tissue compression following hemorrhage [40]. Furthermore, activated blood may contain factors which are toxic to the parenchymal milieu and have been proposed to include excess glutamate, proapoptotic mediators (TNFα and Fas ligand), thrombin, hemoglobin and iron sulfate [41]. Figure 1 provides an overall summary demonstrating the possible outcomes of vessel recanalization following acute ischemic stroke, whether that becomes successful and salvages tissue, leads to no-reflow or results in the deleterious outcome of reperfusion injury.



The outcomes of recanalization following vessel occlusion. In a percentage of patients, both recanalization and reperfusion are successful and lead to tissue salvage and recovery. The no-reflow phenomenon occurs when, in spite of successful mechanical recanalization, no flow is restored to the ischemic tissue bed and is thought in part to be a result of downstream vascular resistance. The third scenario, which has been demonstrated widely in animal models of stroke, is the instance where recanalization and reperfusion are both successful. However, the outcome is cell death or hemorrhagic transformation rather than tissue salvage.

Conclusion

Symptomatic hemorrhagic transformation rates within 24-36 hours of stroke are increased in the setting of revascularization therapy, regardless of modality (ie, intravenous lytics, intra-arterial lytics, antithrombotics, or mechanical devices) [42]. In the absence of revascularization therapy, hemorrhagic transformation is a common and natural consequence of infarction [43].

Rates of symptomatic intracerebral hemorrhage are generally higher in intra-arterial lytic trials [44] (eg, 10% in PROACT-II) than in intravenous lytic trials (eg, 6.4% in NINDS). The rates of symptomatic ICH following revascularization with a device are even lower and range from 4%-2% with the Trevo and Solitaire stent systems, respectively [45].

Hemorrhagic transformation is now known to be a multifactorial process. Stroke severity is likely to be a major predictor of symptomatic intracerebral hemorrhage because it is associated with the volume of ischemic brain at risk for hemorrhagic transformation. Older patients may be at greater risk of symptomatic intracerebral hemorrhage. Higher lytic doses are associated with higher symptomatic intracerebral hemorrhage risk, but whether lower doses can achieve adequate benefit with less risk is not known. Delayed revascularization minimizes benefit and likely increases risk. The goal of acute revascularization should not just be to open occluded vessels but to open them quickly. Patient selection based on physiologic parameters is likely important to reduce late hemorrhage attributable to revascularization.

Transcranial Doppler (TCD) ultrasonography measures cerebral blood flow in major cerebral arteries. Low preoperative distal carotid artery pressure (< 40 mm Hg) and an increased peak blood flow velocity have been found to be predictive of postoperative hyperperfusion [46]. Therefore, TCD can be used to select patients for aggressive postprocedure observation and management. In a patient who is determined to be at risk, TCD can also be used during the postoperative period to assess for hyperperfusion.

The most important factor in preventing reperfusion syndrome is early identification and control of hypertension [47]. This is important even in normotensive patients, since delayed hypertension can occur. The use of TCD ultrasonography preoperatively and postoperatively can aid in identifying patients with increased CBF and, consequently, increased risk of hyperperfusion. Blood pressure should then be controlled aggressively if CBF elevates.

In the situation of reperfusion after carotid endarterectomy (CEA), Cleveland Clinic has implemented an effective protocol for identifying risk factors of reperfusion syndrome and post-op hemorrhage. These risk factors include stenosis of >80%, pre-morbid hypertension, and poor collaterals. In these patients the BP was maintained at less than 120/80 post-op. Of 225 patients, 33% (n=75), 0 patients had post-op reperfusion syndrome, or hemorrhage. Prior to the protocol implementation they had a 17% complication rate.

Pressures can be reduced gently with antihypertensives that do not increase CBF or cause excessive vasodilatation. Examples include labetalol and nicardipine. Less favored medications include intravenous angiotensin-converting enzyme (ACE) inhibitors, calcium-channel blockers, and vasodilators such as nitroprusside [48].

Unfortunately, no specific parameters or guidelines

have yet been established for optimal blood pressure under these circumstances. According to the American Stroke Association stroke and intracerebral hemorrhage guidelines, the blood pressure goal for an acute intracerebral hemorrhage is a mean arterial pressure (MAP) of less than 110 mm Hg [49]. This modest pressure goal can also be applied in acute ischemic stroke with reperfusion issues, because it does not hypoperfuse the tenuous surrounding tissues, nor does it further aggravate injury or hemorrhagic conversion.

In any case, it remains the consensus that patients should be observed postoperatively in an intensive care unit (ICU) setting. If blood pressure management is an issue, it should be managed in the ICU until stabilized.

References

1. Schaller B, Graf R. Cerebral ischemia and reperfusion: the pathophysiologic concept as a basis for clinical therapy. J Cereb Blood Flow Metab 2004; 24:351–371.
2. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995; 333:1581–1587.
3. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. Stroke 1997; 28:2109–2118.
4. Aronowski J, Strong R, Grotta JC. Reperfusion injury: demonstration of brain damage produced by reperfusion after transient focal ischemia in rats. J Cereb Blood Flow Metab 1997; 17:1048–1056.
5. Yang GY, Betz AL. Reperfusion-induced injury to the blood-brain barrier after middle cerebral artery occlusion in rats. Stroke 1994; 25:1658–1665.
6. Dietrich WD. Morphological manifestations of reperfusion injury in brain. Ann N Y Acad Sci 1994; 723:15–24.
7. Kuroda S, Siesjo BK. Reperfusion damage following focal ischemia: pathophysiology and therapeutic windows. Clin Neurosci 1997; 4:199–212.
8. Gobin YP, Starkman S, Duckwiler GR et al. A phase 1 study of mechanical embolus removal in cerebral ischemia. Stroke 2004; 35:2848–2854.
9. Martinez H, Zoarski GH, Obuchowski AM et al. Mechanical thrombectomy of the internal carotid artery and middle cerebral arteries for acute stroke by using the retriever device. AJNR Am J Neuroradiol 204; 25:1812–1815.
10. Paulson OB, Strandgaard S, Edvinsson L: Cerebral autoregulation. Cerebrovasc Brain Metab Rev 1990; 2:161-192.
11. Shapiro HM, Stromberg DD, Lee DR, Wiederhielm CA: Dynamic pressures in the pial arterial microcirculation. Am J Physiol 1971; 221:279-283.
12. Broughton BRS, Reutens DC, Sobey CG: Apoptotic mechanisms after cerebral ischemia. Stroke 2009; 40:e331-e339.
13. Taylor RC, Cullen SP, Martin SJ: Apoptosis: controlled demolition at the cellular level. Nat Rev Mol Cell Biol 2008; 9:231-241.
14. Balasubramanian K, Schroit AJ: Aminophospholipid asymmetry: a matter of life and death. Annu Rev Physiol 2003; 65:701-734.
15. Zhang Y, Stevenson GD, Barber C, Furenlid LR, Barrett HH, Woolfenden JM, Zhao M, Liu Z: Imaging of rat cerebral ischemia-reperfusion injury using 99mTc-labeled duramycin. Nucl Med Biol 2013; 40: 80-88.
16. Ay H, Oliveira-Filho J, Buonanno FS, Ezzeddine M, Schaefer PW, Rordorf G, Schwamm LH, Gonzalez RG, Koroshetz WJ: Diffusion-weighted imaging identifies a subset of lacunar infarction associated with embolic source. Stroke 1999; 30:2644-2650.
17. Syrjänen J: Infection as a risk factor for cerebral infarction. Eur Heart J 1993; 14(suppl K):17
18. Chen GY, Nuñez G: Sterile inflammation: sensing and reacting to damage. Nat Rev Immunol 2010; 10:826-837.
19. Eltzschig HK, Eckle T: Ischemia and reperfusion - from mechanism to translation. Nat Med 2011;17: 1391-1401.
20. Hotchkiss RS, Strasser A, McDunn JE, Swanson PE: Cell death. New Engl J Med 2009; 361:1570-1583.
21. Elliott MR, Chekeni FB, Trampont PC, Lazarowski ER, Kadl A, Walk SF, Park D, Woodson RI, Ostankovich M, et al: Nucleotides released by apoptotic cells act as a find-me signal to promote phagocytic clearance. Nature 2009; 461:282-286.
22. Peters O, Back T, Lindauer U, Busch C, Megow D, Dreier J, Dirnagl U: Increased formation of reactive oxygen species after permanent and reversible middle cerebral artery occlusion in the rat. J Cereb Blood Flow Metab 1998; 18:196-205.
23. Olmez I, Ozyurt H: Reactive oxygen species and ischemic cerebrovascular disease. Neurochem Int 2012; 60:208-212.
24. Vitturi DA, Patel RP: Current perspectives and challenges in understanding the role of nitrite as an integral player in nitric oxide biology and therapy. Free Radic Biol Med 2011; 51:805-812.
25. Li J, Zhang H, Zhang C: Role of inflammation in the regulation of coronary blood flow in ischemia and reperfusion: mechanisms and therapeutic implications. J Mol Cell Cardiol 2012; 52:865-872.

26. Kietadisorn R, Juni RP, Moens AL: Tackling endothelial dysfunction by modulating NOS uncoupling: new insights into its pathogenesis and therapeutic possibilities. Am J Physiol Endocrinol Metab 2012; 302:E481-E495.

27. Rodriguez F, Bonacasa B, Fenoy FJ, Salom MG: Reactive oxygen and nitrogen species in the renal ischemia/reperfusion injury. Curr Pharm Des 2013; 19:2776-2794.

28. Yemisci M, Gursoy-Ozdemir Y, Vural A, Can A, Topalkara K, Dalkara T: Pericyte contraction induced by oxidative-nitrative stress impairs capillary reflow despite successful opening of an occluded cerebral artery. Nat Med 2009; 15:1031-1037.

29. Dirnagl U, Iadecola C, Moskowitz MA: Pathobiology of ischaemic stroke: an integrated view. Trends Neurosci 1999; 22:391-397.

30. Lee JM, Grabb MC, Zipfel GJ, Choi DW: Brain tissue responses to ischemia. J Clin Invest 2000; 106:723-731.

31. Prabhakaran S, Naidech AM: Ischemic brain injury after intracerebral hemorrhage: a critical review. Stroke 2012; 43:2258-2263.

32. Pun PB, Lu J, Moochhala S: Involvement of ROS in BBB dysfunction. Free Radic Res 2009; 43:348-364.

33. Wolburg H, Noell S, Mack A, Wolburg-Buchholz K, Fallier-Becker P: Brain endothelial cells and the glio-vascular complex. Cell Tissue Res 2009; 335:75-96

34. Kahles T, Brandes RP: NADPH oxidases as therapeutic targets in ischemic stroke. Cell Mol Life Sci 2012; 69:2345-2363.

35. Bektas H, Wu T-C, Kasam M, Harun N, Sitton CW, Grotta JC, Savitz SI: Increased blood-brain barrier permeability on perfusion CT might predict malignant middle cerebral artery infarction. Stroke 2010; 41:2539-2544.

36. Siesjö BK: Pathophysiology and treatment of focal cerebral ischemia. Part I. Pathophysiology. J Neurosurg 2008; 108:616-631.

37. Phillips SJ, Whisnant JP: Hypertension and the brain. The National High Blood Pressure Education Program. Arch Intern Med 1992; 152:938-945.

38. Euser AG, Cipolla MJ: Cerebral blood flow autoregulation and edema formation during pregnancy in anesthetized rats. Hypertension 2007; 49:334-340.

39. Wang X, Lo EH: Triggers and mediators of hemorrhagic transformation in cerebral ischemia. Mol Neurobiol 2003; 28:229-244.

40. Golding EM: Sequelae following traumatic brain injury. The cerebrovascular perspective. Brain Res Brain Res Rev 2002; 38:377-388.

41. Striggow F, Riek M, Breder J, Henrich-Noack P, Reymann KG, Reiser G: The protease thrombin is an endogenous mediator of hippocampal neuroprotection against ischemia at low concentrations but causes degeneration at high concentrations. Proc Nat Acad Sci USA 2000; 97: 2264-2269.

42. Khatri P, Wechsler LR, Broderick JP. Intracranial hemorrhage associated with revascularization therapies. Stroke. 2007 Feb; 38(2):431-40.

43. Larrue V, von Kummer R R, Müller A, Bluhmki E. Risk factors for severe hemorrhagic transformation in ischemic stroke patients treated with recombinant tissue plasminogen activator: a secondary analysis of the European-Australasian Acute Stroke Study (ECASS II). Stroke. 2001 Feb; 32(2):438-41.

44. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. The NINDS t-PA Stroke Study Group. Stroke. 1997 Nov; 28(11):2109-18.

45. Nogueira RG, Lutsep HL, Gupta R, Jovin TG, Albers GW, Walker GA, et al. Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. Lancet. 2012 Oct 6; 380(9849): 1231-40.

46. Jansen C, Sprengers AM, Moll FL, Vermeulen FE, Hamerlijnck RP, van Gijn J, et al. Prediction of intracerebral haemorrhage after carotid endarterectomy by clinical criteria and intraoperative transcranial Doppler monitoring: results of 233 operations. Eur J Vasc Surg. 1994 Mar; 8(2):220-5.

47. Abou-Chebl A, Yadav JS, Reginelli JP, Bajzer C, Bhatt D, Krieger DW. Intracranial hemorrhage and hyperperfusion syndrome following carotid artery stenting: risk factors, prevention, and treatment. J Am Coll Cardiol. 2004 May 5.

48. [Guideline] Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke. 2007 May; 38(5): 1655-711.

49. [Guideline] Broderick J, Connolly S, Feldmann E, Hanley D, Kase C, Krieger D, et al. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. Stroke. 2007 Jun; 38(6):2001-23.