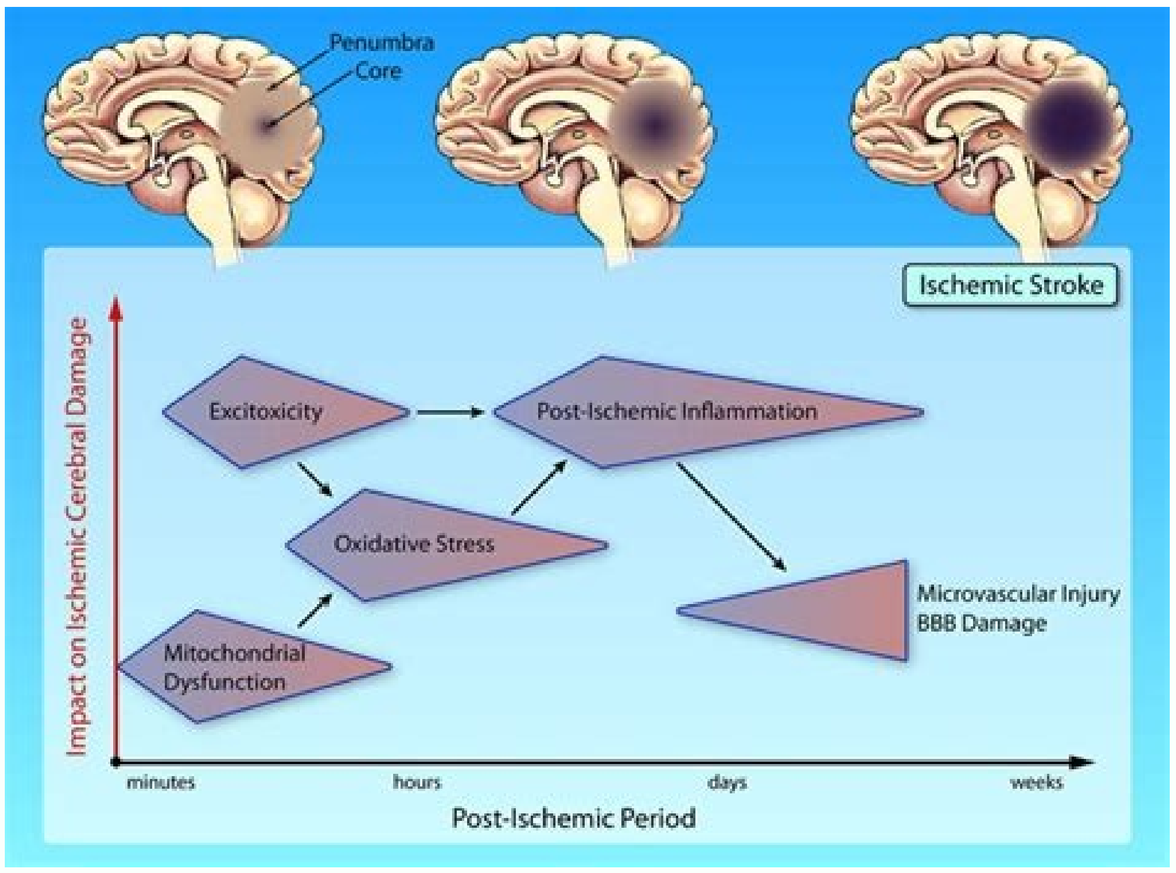
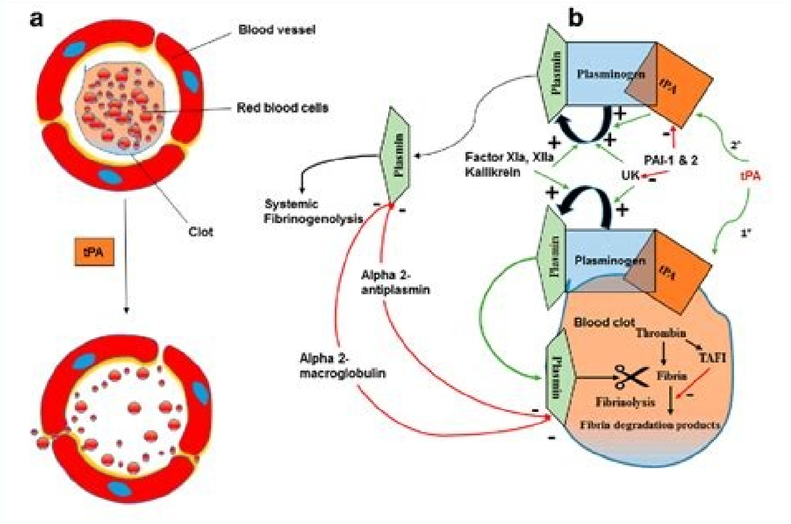
Cerebral ischemic stroke pdf





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Review article

Collaterals in ischemic stroke

Konark Malhotra [a,*], David S. Liebeskind [b,*]

[a] Department of Neurology, Charleston Area Medical Center, West Virginia University – Charleston Division, WV 25301, USA
[b] Department of Neurology and Neurovascular Imaging Research Core, University of California at Los Angeles, Los Angeles, CA 90095, USA

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ABSTRACT

Collateral flow plays a pivotal role, both in acute and chronic phases of cerebral ischemia. Recruitment of these redundant vascular networks maintains cerebral blood flow to ischemic areas, while primary arterial conduits are obstructed either due to steno-occlusive or acute occlusive lesion. Until recently, a heavy focus had been placed solely on such impaired antegrade flow, while the contribution from primary and secondary collateral pathways has been largely disregarded. Imaging of the brain with focus on delineating the collateral circulation has been critical to interpret the mechanism of vascular remodeling that occurs with ischemic injury. Recent multimodal imaging modalities have encouraged physicians to assess collateral flow and hemodynamics from a temporal perspective, distinguishing individual cases to tailor the treatment. Collateral status varies among individuals, correlating with stroke severity and reperfusion outcomes. While new techniques to enhance collateral flow have been speculative, we provide a comprehensive review on the role of collaterals and its therapeutic applications during cerebral ischemia.

1. Introduction

Acute ischemic stroke (AIS) has a high recurrence rate with an elevated global burden of stroke that mandates aggressive evaluation and management from the moment of symptom onset.[1,2] Cerebral ischemia results from acute arterial occlusion or severe narrowing leading to impaired delivery of blood flow. Collateral circulation is a dynamic system that tends to preserve cerebral perfusion in conjunction with pathophysiologic changes. Recruitment of these anastomotic pathways is a major component of cerebral homeostatic response to ischemia when the primary conduits fail to provide perfusion to critical parts of the brain.[3]

Cerebral collaterals are alternate arterial routes that come into play when primary antegrade blood flow is obstructed. These anastomotic conduits include the relatively more proximal 'primary collaterals' as a part of the circle of willis (COW), while their distal counterpart include leptomeningeal or pial vessels that are referred as 'secondary collaterals'.[4] Primary collaterals include anterior and posterior communicating arteries that supply blood flow to large portions of cerebral hemispheres in both anterior and posterior circulations during acute ischemia. Secondary collaterals, comprising of leptomeningeal vessels and ophthalmic artery, are less direct and diminutive connections that evolve gradually and provide added support at times of cerebral ischemia. These form anastomotic connections between internal and external carotid artery via middle meningeal, occipital, facial, and maxillary arteries. Leptomeningeal collaterals are present over the pial surface and anastomose with small distal cortical vessels during ischemic event. Acute cerebral ischemia usually triggers the recruitment of both Willisian collaterals that provide flow to adjoining territories as well as leptomeningeal vessels that supply cortical blood flow in a retrograde fashion. Similarly, venous collaterals work as a major element to maintain the cerebral blood volume, a critical variable that quantifies the amount of nutrient blood for the ischemic brain. Along the microcirculation and venous outflow, recent studies have discovered network of lymphatic channels that exist the skull base along sinuses and cranial nerves.[5]

Beyond the existence of these robust anastomotic pathways, development of new vessels has been studied that arise from pre-existing vascular structures secondary to any ischemic insult as an inciting factor.[6] This process of arteriogenesis is propagated by the release of vascular growth factors and is driven by pressure gradient between proximal high and distal low perfusion regions.[7] Development of new arterioles most commonly occurs in chronic cerebral ischemic lesions rather acute arterial occlusions.[8] With time, these small vessels tend to develop layer of smooth muscle and reforms to evolve into large caliber vessels.[9]

Collateral channels in conjunction with impaired anterograde flow determine the evolution of cerebral ischemia. Acute arterial occlusion exerts ischemic demand on collateral channels, while

* Corresponding author.
E-mail address: dliebeskind@mednet.ucla.edu (D.S. Liebeskind).

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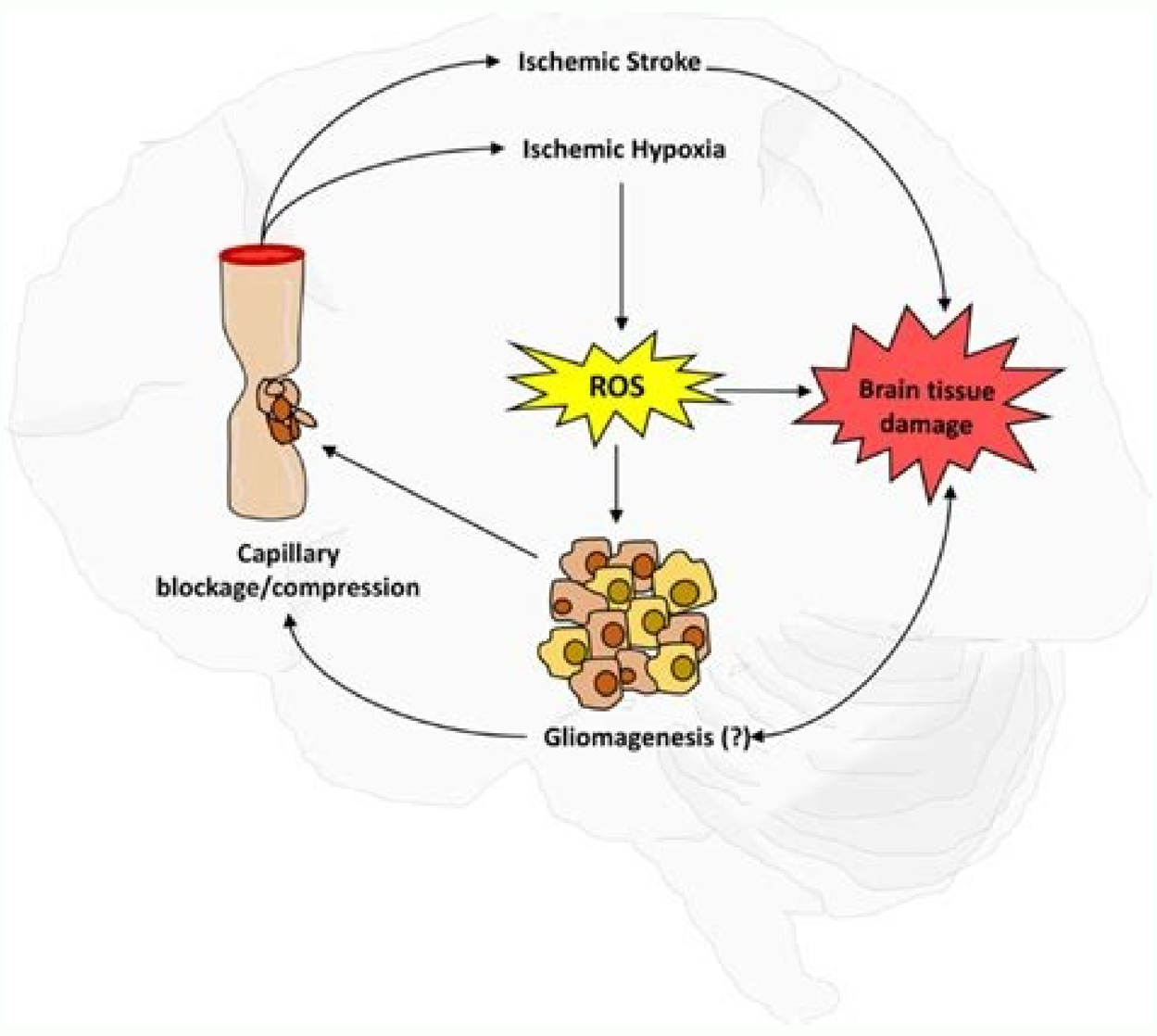

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REVIEW ARTICLE

The role of the cerebral capillaries in acute ischemic stroke: the extended penumbra model

Leif Østergaard[1,2], Sune Nørhøj Jespersen[2,3], Kim Mouridsen[2], Irene Klærke Mikkelsen[2], Kristjana Ýr Jonsdottir[2,4], Anna Tietze[1,2], Jakob Udby Blicher[2,5], Rasmus Aamand[2], Niels Hjort[2,6], Nina Kerting Iversen[2], Changsi Cai[2], Kristina Dupont Hougaard[2,6], Claus Z Simonsen[2,6], Paul Von Weitzel-Mudersbach[6], Boris Modrau[7], Kartheeban Nagenthiraja[2], Lars Riisgaard Ribe[2], Mikkel Bo Hansen[2], Susanne Lise Bekke[2], Martin Gervais Dahlman[2], Josep Puig[8], Salvador Pedraza[8], Joaquín Serena[9], Tae-Hee Cho[10], Susanne Siemonsen[11], Götz Thomalla[12], Jens Fiehler[11], Norbert Nighoghossian[10] and Grethe Andersen[6]

The pathophysiology of cerebral ischemia is traditionally understood in relation to reductions in cerebral blood flow (CBF). However, a recent reanalysis of the flow-diffusion equation shows that increased capillary transit time heterogeneity (CTTH) can reduce the oxygen extraction efficacy in brain tissue for a given CBF. Changes in capillary morphology are typical of conditions predisposing to stroke and of experimental ischemia. Changes in capillary flow patterns have been observed by direct microscopy in animal models of ischemia and by indirect methods in humans stroke, but their metabolic significance remain unclear. We modeled the effects of progressive increases in CTTH on the way in which brain tissue can secure sufficient oxygen to meet its metabolic needs. Our analysis predicts that as CTTH increases, CBF responses to functional activation and to vasodilators must be suppressed to maintain sufficient tissue oxygenation. Reductions in CBF, increases in CTTH, and combinations thereof can seemingly trigger a critical lack of oxygen in brain tissue, and the restoration of capillary perfusion patterns therefore appears to be crucial for the restoration of the tissue oxygenation after ischemic episodes. In this review, we discuss the possible implications of these findings for the prevention, diagnosis, and treatment of acute stroke.

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Keywords: acute ischemic stroke; capillary transit time heterogeneity (CTTH); cerebrovascular reserve capacity (CVRC); penumbra; reperfusion injury; stroke risk factors

INTRODUCTION

The pathophysiology of cerebral ischemia is traditionally understood in relation to specific cerebral blood flow (CBF) thresholds. The term ischemia (from Greek: *isch*—restriction; *aimia*—blood) therefore refers to a reduction in CBF that causes the cessation of neuronal electrical activity in experimental ischemia and the sudden appearance of focal neurologic symptoms in patients. The corresponding CBF threshold is ~ 20 mL/100 mL per minute, both in humans and across a number of animal species.[1] Below CBF levels of 8 to 12 mL/100 mL per minute, oxygen supplies no longer suffice to fuel vital cell functions such as the maintenance of ion homeostasis across cell membranes, and brain tissue therefore suffers permanent damage, infarction, within minutes.[2] At CBF values above this level, ischemic tissue may survive for several hours and regain function if CBF is normalized. Such impaired, yet salvageable tissue is referred to as the *ischemic penumbra*[3,4] and characterized by elevated oxygen extraction fraction (OEF).[4] The concept of an ischemic penumbra that can be salvaged by early vessel recanalization has been highly successful in that placebo-controlled trials have shown a reduction in neurologic deficits in acute stroke patients treated by intravenous recombinant tissue plasminogen activator during the first hours after symptom onset.[5–8]

Resting CBF in human gray matter is in the range of 40 to 70 mL/100 mL per minute and the etiology of ischemic stroke is therefore linked to conditions that can cause significant reductions in regional CBF. Before the stroke, most stroke patients have had combinations of large-vessel stenoses, small vessel disease (SVD), and a propensity to form either cardiac emboli or arterial thrombi in relation to atherosclerotic lesions[9]—see Figure 1.

[1]Department of Neuroradiology, Aarhus University Hospital, Aarhus, Denmark; [2]Center of Functionally Integrative Neuroscience and MINDLab, Department of Clinical Medicine, Aarhus University, Aarhus, Denmark; [3]Department of Physics and Astronomy, Aarhus University, Aarhus, Denmark; [4]Department of Mathematics—Centre for Stochastic Geometry and Advanced Bioimaging, Aarhus University, Aarhus, Denmark; [5]Research Unit, Hammel Neurorehabilitation and Research Centre, Aarhus University Hospital, Hammel, Denmark; [6]Stroke Unit, Department of Neurology, Aarhus University Hospital, Aarhus, Denmark; [7]Department of Neurology, Aalborg University Hospital, Aalborg, Denmark; [8]Department of Radiology, Girona Biomedical Research Institute, Hospital Universitari de Girona Dr Josep Trueta, Universitat de Girona, Girona, Spain; [9]Department of Neurology, Girona Biomedical Research Institute, Hospital Universitari de Girona Dr Josep Trueta, Universitat de Girona, Girona, Spain; [10]Cerebrovascular Unit, Hôpital Neurologique Pierre Wertheimer, Lyon, France; [11]Department of Diagnostic and Interventional Neuroradiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany and [12]Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. Correspondence: Professor L Østergaard, CFIN/Department of Neuroradiology, Aarhus University Hospital, Building 10 G, 5th Floor, Nørrebrogade 44, Aarhus C 8000, Denmark.
E-mail: leif@cfin.dk
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Molecular Therapy 26(10):2333–2334. ➔ Article PubMed PubMed Central Google Scholar Page 2 Skip to main content From: Cerebral ischemic stroke and different approaches for treatment of stroke Name of drug Mechanism of action as neuroprotection Remark Selfotel Competitive glutamate receptor antagonist Phase III trial stopped because of adverse effects Eliprodil Glutamate antagonist at polyamine modulator site Phase III trial ceased due to no efficacy Aptiganel Noncompetitive NMDA channel blocker Ineffective for acute stroke therapy in phase III trial LeukArrest Anti-inflammatory monoclonal antibodies Phase III trial stopped because of unfavorable results Fosphenytoin Sodium channel blocker and blocks calcium ions entry also Phase III trial stopped due to non-beneficial results Maxipost Potassium channel activator Phase III trial results fail Citicoline Membrane stabilization and improvement in infarct size Ineffective in phase III trial Clomethiazole Gamma-amino butyric acid receptor antagonist Phase III trial aborted due to response failure from the patient Repinotan Serotonin agonist Phase II trial shows neuroprotective effect

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