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Collateral Flow: Prolonging the Ischemic Penumbra

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Abstract

This editorial serves as an introduction to the Special Issue on Collateral Flow: Prolonging the Ischemic Penumbra

The mindset of stroke care has shifted over the past four decades from one of perceived therapeutic nihilism to a reperfusion-oriented interventional approach. In parallel with this remarkable transformation in the stroke landscape has been the realization that the cerebral collateral circulation is critically important to stroke pathophysiology and outcomes. Experimental studies dating back five or six decades suggested a distinction between an ischemic core and a potentially salvageable penumbra (1), coupled with primate studies measuring cerebral blood flow in these zones after large vessel occlusion (2). In the 1980s, the proposal that thrombolysis was a viable option for stroke by Del Zoppo and others was predicated on existence of collateral flow to a salvageable penumbra that afforded precious time to intervene (3).

The idea that alternate endogenous pathways may be recruited to bypass acute or chronic stenoses or occlusions is not new; Denny-Brown commented on the importance of collaterals and the ability of hemodynamic manipulations to improve ischemic symptoms in 1957 (4). In fact, he made the statement, “In embolism the area of infarction is also greatly variable, manifestly due to variations in collateral supply. It is, therefore, desirable to learn more of the dynamic adjustments of collateral vessels in the brain …” (5). However, scientific investigation advanced in fits and starts through the latter part of the twentieth century, but has risen exponentially over the past decade with the rise of endovascular interventions, now with over 300 papers being published annually on the cerebral collateral circulation and stroke.

Advances in imaging now allow visualization of the occlusion, associated cerebral vascular anatomy and the perfusion status of each patient accelerated the transformation to precision stroke care. Penumbral imaging extended the thrombolytic window to nine hours in select

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patients (6). Similarly, targeted patient selection for thrombectomy of large vessel occlusions based on status of the penumbra was proven in landmark studies (7, 8). This heterogeneity in penumbral dynamics was attributed to the fact that collateral circulation and its recruitment in the face of occlusion differed widely between patients.

With the realization that understanding collaterals would enable more precise therapeutic selection and prognostication, came the drive to understand the pathophysiology of the collateral circulation and how it can be measured and manipulated. It is toward that goal that this Special Issue of *Translational Stroke Research* was conceived. We sought to bring together experts in various aspects of the cerebral collateral circulation to write authoritative reviews summarizing the scientific knowledge in these domains, focusing on how this system contributes to the *Evolving Ischemic Penumbra*.

The issue opens with a comprehensive review by Liebeskind and Patel that covers the anatomy of the cerebral collateral circulation, an up-to-date summary of the evolving imaging tools to measure collaterals and the penumbra, and its relevance to acute stroke. The review by Heit and Seifert builds upon this introduction with a review of the concepts and literature surrounding how collateral status contributes to early infarct growth (9). This paper also explores how novel tissue-based collateral indices like hypoperfusion intensity ratio may provide information that assists in selection and prognostication, including of complications like cerebral edema (10). The third review provides a systematic review the impact of collateral status on outcomes after thrombectomy (11). The relevance of collaterals may be particularly important in intracranial atherosclerotic disease where stroke recurrence can be high, as reviewed by Leng and Leung (12). Finally, Dr. Marilyn Cipolla provides an overview of how we may be able to intervene to augment the collateral circulation, preserve the penumbra (for example, before reperfusion can occur), and prevent irreversible injury (13). A recent open submission to the journal also addresses how agents to enhance cerebral blood flow act through augmenting collateral flow (14).

In conclusion, significant advances have been made in understanding the impact of collateral flow in stroke, but this arena of investigation is very much in evolution. We still need to understand more completely the key environmental and genetic factors that explain why one person experiencing a stroke has good versus poor collaterals. Polymorphisms in the *Rabep2* gene have been demonstrated to influence collateral extent and the severity of resultant stroke in mice (15). Preliminary studies have begun to address biologic influences in humans, but much more work is still needed (16). Large collaborative groups have begun to address the genetic architecture of collaterals and other acute stroke traits in humans (17).

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