

The Challenges of Microvascular Disease in the Era of Endovascular Thrombectomy

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Introduction

We are facing an extremely exciting era after knowing the results of the recently finished clinical trials on the effectiveness of endovascular thrombectomy in acute stroke patients with large vessel occlusion [1-3]. The MRCLEAN, ESCAPE, EXTEND-IA and SWIFT-PRIME trials showed that a significant proportion of patients with acute stroke may greatly benefit from endovascular thrombectomy with the current generation of stentriever devices and these results are expected to be confirmed by the REVASCAT trial [4] to be presented in the upcoming European Stroke Organization Conference in Glasgow next April. One of the most interesting aspects of these studies is that patients with poor prognostic factors such as advanced age or tandem occlusions also benefit from endovascular thrombectomy, because their functional outcome is terrible when only medical therapy is used.

Despite all these positive results, it is important to be aware that many stroke patients won't benefit from these acute revascularization therapies, for example patients arriving too late to the hospital. Moreover, half of all stroke patients present with mild symptoms and the benefits of endovascular therapy are not clear in these patients. In contrast with the increasingly recognized efficacy of intravenous thrombolysis in patients with mild strokes [5], in a study analyzing all patients with mild strokes in a prospective registry in the region of Catalonia endovascular treatment was not associated to greater chances of full recovery [6], suggesting that the risk/benefit ratio is not favorable enough in these patients. Even if most of the recent trials had quite unrestricted inclusion criteria regarding symptom severity, most of the patients treated in those trials had moderate to severe strokes with median NIHSS scores of 16 to 17.

Moving from a symptomatic definition to a more pathological one of minor stroke, it should not be surprising that the extremely extensive network of small vessels in the brain may affect the hemodynamics of greater more visible vessels and even influence the fate of the brain in ischemic conditions. Thus, even if intravenous thrombolysis is safe in patients with small vessel disease [7], the extent of leukoaraiosis is associated to final stroke volume and poor outcome [8] also after endovascular revascularization therapies [9].

The capillary bed of the brain is comprised of a dense network of intercommunicating vessels [10] and in rodents dilation in capillaries after penetrating arteriole occlusion allows some collateral flow from one arteriolar territory to neighbor territories [11]. In agreement with these findings, we have recently shown in humans that small lacunar infarcts have similar perfusion characteristics compared to major vessels in the brain, suggesting that the hemodynamic abnormalities of lacunar infarcts although small are very similar to those described in infarcts resulting from occlusion of greater vessels [12].

Just as some intracranial vascular malformations such as dural arterio-venous fistulas can be cured by destroying the venous outflow of the malformation, it is possible that radiologically visible arterial collaterals are reflecting to a great extent what is going on in smaller ubiquitous blood vessels. Accordingly, increasing leukoaraiosis was independently associated to poor collateral grade in a cohort of

stroke patients receiving endovascular interventions [13]. Thus, the huge prognostic significance of collateral flow in these patients may not only reflect the hemodynamic wellbeing of the ischemic tissue but also the integrity of the neurovascular unit at a smaller physiologically even more relevant scale.

The pathophysiological aspects of small vessel disease in acute cerebral ischemia are very rich and diverse. In fact, it is very possible that many neuro protectants may be acting through protecting the micro vessels. Inflammation is an important pathological mechanism after stroke and many studies linked excessive inflammation with poor outcome after stroke. However, a recent study that showed little leukocyte extravasation after cerebral ischemia [14]. Some deleterious effects of inflammation could be explained by the non-reflow phenomenon that could explain poor perfusion because of leukocyte accumulation in the small vessels in the brain. Yet we have recently described an alternative mechanism of leukocyte infiltration into the ischemic brain, showing both in human and rodent samples that granulocytes predominantly reach the ischemic tissue from the cortical vessels and traveling through the perivascular space of penetrating arteries [15]. Once in the ischemic venules, recruited neutrophils scan for activated platelets, integrating signals present at both the endothelium and the circulation and initiating thrombo inflammatory injury [16]. Elucidating the details of the inflammatory mechanisms affecting the neurovascular unit is of course crucial for the development of immune modulating therapies that have failed until now.

In conclusion, while it is exciting to finally use endovascular therapy in stroke patients, there are still many patients that can't be cured even when thrombectomy is used. All the diverse and active processes going on at smaller scale micro vessels offer the potential for therapies that will be acting in a huge network of vessels in close contact to the rest of the actors of the neurovascular unit, and these therapies will hopefully benefit a great proportion of stroke patients in the future either alone or in combination with revascularization therapies. Previous failures in anti-inflammatory, immune modulatory and neuro protectant therapies most likely reflect insufficient knowledge of these mechanisms and the use of the wrong medications, just as endovascular therapy of acute stroke failed until increasing experience and the development of modern thrombectomy devices resulted in definitely positive clinical trials.

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