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EDITORIAL

# Pretherapeutic characterization of the clot in acute stroke

Now, one year after ground-breaking publications regarding the safety and efficacy of endovascular techniques in acute stroke [1—4], it seems to be even more important to assess the diagnostic tools at our disposal to help select patients for treatment [5,6].

Over the last two decades, the progress in treatment has been paralleled by advances in diagnostic techniques: during the decade of the brain, right after the first studies which demonstrated the utility of intravenous thrombolysis [7,8] both computed tomography (CT) and magnetic resonance (MR) underwent technological breakthroughs that allowed an earlier diagnosis of ischemia than had previously been possible [9,10]: by using techniques such as diffusion MR and perfusion CT one could demonstrate changes associated with ischemia well within the therapeutic window (initially at 3 hours after onset).

Until then, imaging in stroke had been either used to detect life-threatening massive hemorrhage or as a mere documentation of infarcts in patients that would result in long-term rehabilitation.

Over the last few years, at least in the neuroradiological community, we have seen an acceptance of a shift from intravenous therapy to an initial intra-arterial local fibrinolysis and now to mechanical thrombectomy [11].

This has not been without controversy, many authors were previously reluctant to support endovascular techniques due to negative early reports [12,13] that not only showed a non-superiority of endovascular techniques over the accepted intravenous therapy but also showed that thrombectomy and imaging selection were useless [14,15]. This was contrary to what many in the interventional world believed [16] and which would lead to further investigation using improved clinical trials with improved newer generations of endovascular tools.

However with the publication of the recent positive trials for endovascular techniques, growing evidence has accumulated that these technologies can now safely treat stroke and probably provide improved outcomes [17], mainly with clot extraction using also imaging techniques for patient selection.

After some disappointment in reported trials, the MR CLEAN study demonstrated that endovascular treatment has had a positive impact on recanalization [17,18], this was later supported by the subsequent studies such as the REVASCAT, SWIFT PRIME and ESCAPE trials [1—3,19].

Thus, since mechanical clot extraction is now the method that now seems to becoming more and more popular as an undisputed method of treatment, there is increased evidence showing that we now need to better image the embolus itself in order to select patients for thrombectomy [20].

This treatment may be combined with thrombolysis or used alone as primary treatment. What seems to be increasingly important to consider is that clot composition itself may have an implication on the chosen therapy [21] and that it would be helpful to be able to characterize clot composition by imaging.

It must be noted that CT has been able to demonstrate vascular hyperdensity for decades and the so-called dense artery sign (called the dense artery sign, hyperdense artery sign or even the dot sign) is a known sign of acute stroke [22—24]. This sign is now found to be present increasingly in the affected vessel of patients with the use of high resolution CT with thin slices and remains a strong indicator of stroke [25,26].

Hopefully this should also allow differentiating between red and white clots. Indeed, from the hematological literature, we know that we may find clots that are either composed of mainly red blood cells or of fibrin; due to this the clot one encounters may on the one hand have a different origin (cardiac or carotid) but also a different composition and thus may also react differently depending upon which treatment modality is chosen. Indeed, the dense artery sign we see on CT and the gradient blooming effect visible on T2* MR images reflect an occlusive thrombus. The dense artery sign and the blooming effect on MR seem to

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reflect the red blood cell content, whereas the absence of these signs may signify more fibrin-predominant thrombi [27].

In addition, we now know that clot location length and burden can play an important role in outcome and treatment possibilities [28—30]. Especially Riedel et al. reported that a length of more than 8 mm would indicate no effect of intravenous therapy [31], and overall we have now observed that in patients undergoing endovascular therapy the rate of recanalization decreases proportionally with thrombus length [32,33].

New imaging techniques currently emerging could help better define the composition of the clot. Cerebral clots may contain various degrees of fibrin, calcifications or debris, all of which may respond differently to the different modalities [34].

With this in mind, the more solid or calcific plaques may be more resistant to intravenous pharmacological treatment than those composed predominantly of fibrin [35]. Transcranial Doppler can partly differentiate already between gaseous and embolic material but this is now insufficient or not adequate for the new treatment modalities [36]. What is interesting is that despite the evolution in imaging techniques over the years, their use in trials have lagged behind: indeed while imaging seems undisputed for the early NEJM paper as well as for the recent trials, these have up to now not focused on the clot itself. This seems even stranger knowing that in the recent clot extraction studies, patient selection based on imaging findings was central [4]. In the early stroke studies, rudimentary brain imaging based on unenhanced CT criteria were used for patient selection: the only imaging inclusion criteria was the absence of hemorrhage in the initial studies.

However this is currently in complete opposition with the technical advances that we have known that help us characterize the brain and its vessels. It has become evident that imaging tissue damage (e.g. a large hypodensity or diffusion-weighted lesion) and viability (based on perfusion maps derived from CT or MR perfusion) is now established clearly.

This may not be enough in order to help to determine which method to choose for revascularization since clot length and composition may positively or negatively impact on the effect of a chosen treatment modality.

It is becoming increasingly clear that since clot extraction is the now proposed method, with the corollary that the nature of the clot demonstrated should be improved in order to optimize the choice of the endovascular tool to be employed.

Clot characterization may additionally help determine which clots may benefit from either intravenous treatment alone as well as which clots, because of their composition, may necessitate dedicated retrievers [6].

More emphasis might be put on simple measurements of Hounsfield units on unenhanced CT since clot composition could play a role in patient selection as new evidence points to the fact that clot density may predict its recanalization after therapy and thus have an impact on patient outcomes [37,38].

In a recent study, Uchiyama et al. found that the characterization of the carotid plaque (which is one of the possible causes of embolism) using CT was able to demonstrate that there was a correlation between plaque density and the number of brain lesions [39].

Further emerging imaging technologies such as dual energy-CT techniques could help in improving clot visualization and characterization.

Positron emission tomography (PET) CT techniques that have been utilized may be more exotic and less useful in the acute setting of stroke [40], especially since MR techniques are constantly improving, with the advent of higher field strengths and more advanced sequences [41,42]. These may eventually provide further answers to the nature of the clot.

Stroke MR may also have an additional role in patient selection despite having been somewhat neglected recently [43,44].

Therefore, there is great hope that by improving or adapting imaging modalities, we can detect patients that require a certain type of treatment earlier on. This said, now that we have new endovascular modalities available that facilitate stroke treatment, it is necessary to go beyond simple diagnostic imaging and look among others into the composition of the clot in order to adapt the technique utilized in order to improve recanalization and patient outcomes. Also we must never forget that whenever we are considering these patients for treatment, we cannot just use basic parenchymal imaging, vascular imaging or perfusion techniques but we must use them all together in order to obtain the best idea of what can be done in the least amount of time. Only then will diagnostic methods be ready for the new neuro-interventional age [45].

Thus, we can decide when to extract, what to extract and how to extract the thrombus and not rely on guess-work for what may be the most appropriate method in a very often complicated and serious situation.

## Disclosure of interest

The authors declare that they have no competing interest.

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