Sonothrombolysis: Current status

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\section*{Summary}
This contribution summarizes the past and present status of ultrasound-facilitated thrombolysis (sonolysis) with and without the use of microspheres. Different ultrasound techniques are addressed and advantages as well as pitfalls are discussed.

\section*{Introduction}
Intravenous thrombolysis with rt-PA is the only approved therapy for treating acute ischemic stroke and needs to be administered within the first 4.5 h after symptom onset [1]. Among other factors, the speed and completeness of recanalization, and successive reperfusion of ischemic brain tissue is associated with final infarct size, restoration of function, and finally clinical outcome. With i.v. rt-PA only, there is a rather low percentage of patients achieving early (30–40%) and complete (18%) recanalization [2]. Therefore, various ways to improve speed and completeness of recanalization have been studied, among others the therapeutic use of ultrasound, alone or in combination with thrombolytics. The following brief overview reflects the current clinical status of sonothrombolysis. For an extensive recent review (and the basis for this chapter) including the experimental background of sonothrombolysis the reader is referred to Amaral-Silva et al. [3].

Delivery of tPA to the thrombus is dependent on the residual flow to and around the arterial obstruction, and better residual flow signals detected by Transcranial Doppler (TCD) are associated with higher recanalization rates and consequently better clinical course in stroke patients treated with i.v. tPA [3,4]. Proximal arterial occlusions are a marker of clot burden and poorer response to thrombolysis in terms of recanalization [5,6]. Therefore, proximal intracranial occlusion is a target for more advanced reperfusion strategies, among them ultrasound-enhanced thrombolysis. While several ultrasound techniques have been applied, the focus of this contribution shall remain on the techniques that are also used in standard diagnostic ultrasound, i.e. transcranial color coded duplex (TCCD) and TCD.

TCD is a non-invasive technique that uses ultrasound to access regional blood flow by determining flow velocities of intracranial arteries. TCD is a fast and reliable method of obtaining real-time information on the presence and location of arterial occlusion and recanalization during or shortly after thrombolysis [3]. The patterns of intracranial arterial occlusion and recanalization on TCD have been validated against angiography with high sensitivity and specificity values resulting in the now widely used derived thrombolysis in brain ischemia (TIBI) grading system [7].

\section*{Clinical studies}
High frequencies lead to greater attenuation of ultrasound, lower frequencies may be harmful due to tissue heating. There are only very limited data on the effect of ultrasound
alone (without thrombolytic drugs) to facilitate clot lysis in acute stroke.

The TRUMBI study, a phase II clinical trial testing the use of low frequency ultrasound insonation in acute stroke patients treated with i.v. t-PA, showed a significant increase in hemorrhage, both symptomatic and asymptomatic [8]. The trial included i.v. rt-PA patients within 6 h of symptom onset but was closed early because of signs of ICH in 13/14 patients compared with 5/12 patients on rt-PA only albeit identical recanalization rates. Since then, clinical trials restricted the use of ultrasound for therapeutic purposes to the settings usually used for diagnostic purposes (1–2 MHz), which have proved their safety and efficacy in several experimental and clinical trials.

Alexandrov et al. reported one of the first clinical reports on the use of sonothrombolysis in acute stroke patients [9] and showed with 2 MHz TCD a higher response rate to i.v. t-PA at 24 h than previously documented (40% of patients versus 27% in the NINDS trial showed a >10 points improvement in NIHSS or complete recovery). This pilot trial was followed by a phase II randomized controlled trial CLOTBUST (Combined Lysis of Thrombus in Brain Ischemia using Transcranial Ultrasound and Systemic TPA), which demonstrated that enhancement of the thrombolytic activity of tPA could be safely achieved by using higher frequency (2 MHz) and low intensity (<700 mW/cm²) single element pulsed-wave ultrasound [2]. In 126 patients randomized in a 1:1 fashion acute rt-PA treated stroke patients were either insonated within a 3-h time window for 2 h or not. rt-PA induced arterial recanalization was increased by ultrasound (sustained complete recanalization rates at 2 h: 38% versus 13%, p = 0.002) with a non-significant trend toward an increased rate of clinical recovery from stroke, as compared with placebo and at no increased cost of bleeding complications (4.8% in both arms). A phase III trial has been planned for quite some time and protocols have been published [10]. The problem, however, is still the lack of an investigator independent device, although this may be solved in the close future (Andrei Alexandrov, personal communication).

Transcranial color coded duplex ultrasound (TCCD) has been used in four smaller trials of ultrasound enhanced thrombolysis [3]. In general, the results were somewhat better than control rt-PA patients with regard to recanalization and trends for outcome, but again at the cost of higher bleeding rates fortunately not in the same range as in the TRUMBI trial.

Microbubble-enhanced sonothrombolysis

Microbubbles (MBs, microspheres), originally developed as ultrasound contrast agents, have been utilized for increasing ultrasound performance in neurovascular imaging and sonolysis by enhanced cavitation and microstreaming [11,12]. Derived from experimental studies in the 90s [13], the approach was consecutively applied to the clinical setting [12,14]. In a first study Molina and colleagues used levovist® given at 3 time points in 38 patients compared to 73 patients treated with either 2 MHz TCD and rt-PA or rt-PA alone [12]. Complete recanalization rate 2 h after t-PA bolus was significantly higher in the tPA/US/MB group (54.5%) compared with tPA/US (40.8%) and tPA (23.9%) groups (p = 0.038). No systemic symptoms deriving from MBs use were documented. Symptomatic ICH rates did not differ. A French TCCD (plus rt-PA plus MB versus rt-PA alone) study was terminated prematurely because of safety concerns [15]. Other MBs have been tested but none have emerged so far as superior to others.

Newer submicron lipid coated perfluorcarbon MBs (“nanobubbles”) were tested in a pilot trial and a phase Ila study [14,16]. Preliminary data compared to historic controls from the CLOTBUST trial showed a higher rate of complete recanalization (50% versus 18%, p = 0.028) and sustained complete recanalization at 2 h (42% versus 13%, p = 0.003). Interestingly, in a majority of patients MBs were detected in areas with no pretreatment flow, indicating permeation beyond intracranial occlusions [17].

The phase Ila TUCSON study [14] aimed to determine the safety, tolerability, and activity of perfluorcarbon MBs MRX-801 plus TCD insonation in sonothrombolysis. Thirty-five patients with pretreatment proximal intracranial occlusions on TCD were randomized (2:1 ratio) to increasing doses of MRX-801 MBs infusion over 90 min. The study was terminated prematurely by the sponsor because of bleeding events in the 2nd dose tier, although all the 3 bleedings could have been attributed to very severe strokes and high blood pressures during treatment. Despite that, a trend toward higher sustained complete recanalization rates in both MBs dose tiers compared to control was observed (67% for Cohort 1, 46% for Cohort 2, and 33% for controls, p = 0.255). To date this was the last sonothrombolysis study also using MBs, and the concept remains to be rechallenged in the authors’ opinion.

Conclusions

Early and effective reperfusion is the key for early ischemic tissue rescue and further good clinical outcomes. However, i.v. tPA alone can only accomplish this goal in less than 50% of the patients. Ultrasound may be a tool to enhance clot lysis, albeit the final verdict has to be spoken. At the current stage a phase III trial with an investigator blinded 2 MHz device using the settings of the original CLOTBUST study is underway, and the protocol has been finalized. Future research should be dedicated to optimizing the technical setting of ultrasound, the development of untargeted and targeted MBs and optimizing the feasibility of this not so novel therapeutic approach to acute stroke.

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