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## Commentary on Meunier *et al.*, Temperature Affects Thrombolytic Efficacy Using rt-PA and Eptifibatide, an *In Vitro* Study

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**O**VER THE PAST one or two decades, progress in the treatment of brain ischemia has included the use of recombinant tissue plasminogen activator (rt-PA) to recanalize occluded vessels rapidly in ischemic stroke, and the use of therapeutic cooling to improve neurological outcome following cardiac arrest. Recent clinical studies have focused on the possibility of whether combining both therapies might lead to an even better outcome than either treatment alone.

While it remains to be seen whether therapeutic cooling can actually benefit the ischemic stroke victim, preclinical studies have repeatedly shown that therapeutic hypothermia is more effective when reperfusion occurs (Krieger and Yenari, 2004; van der Worp *et al.*, 2010). Thus it will be important to combine cooling with recanalizing therapies. Rt-PA remains the most commonly used approach, although specialized centers may also be capable of using mechanical thrombectomy devices. Understanding the effect of cooling on the coagulation and fibrinolytic systems is clearly relevant. Surprisingly few studies have been carried out to determine potential interactions between cooling and thrombolysis. Past studies have shown small changes in clot lysis within temperature ranges used clinically, and the extent of recanalization by rt-PA seems to outweigh the small reduction in thrombolysis by cooling (Yenari and Hemmen, 2010). A clinical study suggested that the combination of rt-PA and therapeutic cooling did not increase intracranial hemorrhage risk compared to rt-PA alone (Hemmen *et al.*, 2010).

This study examines the influence of temperature on clot lysis by rt-PA and the novel GP IIb/IIIa inhibitor eptifibatide (Meunier *et al.*, 2012). A well-established “clot on string” model was used to study clots made from human blood samples suspended in plasma and incubated at different temperatures. The rt-PA and eptifibatide were applied in concentrations that corresponded to clinically relevant ranges. The authors found less clot lysis with rt-PA alone and rt-PA plus eptifibatide at lower temperatures, whereas clot lysis in control samples was slightly higher at 30°C compared to 37°C. These observations are consistent with those reported by our group (Yenari *et al.*, 1995). Yet the differences in clot lysis are much more marked in the current study, especially when eptifibatide is added to rt-PA. Such results underscore

the importance of carefully conducted preclinical animal studies to determine the efficacy of such combinatorial treatments. Further, the safety of such combinations needs to be addressed in appropriate animal models. While clot lysis is decreased at lower temperatures, it is well known that clotting factors are inhibited by cooling, and this could lead to worsened hemorrhage. This study is an important step toward the careful design of clinical trials.

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