CLINICAL IMPLICATIONS OF BASIC RESEARCH

The Shear Stress of Busting Blood Clots

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"Clot-busting" fibrinolytic drugs are administered to patients who have had a heart attack or ischemic stroke. These drugs are delivered systemically or, when possible, locally through a catheter placed within the obstructed vessel. Korin and colleagues[1] found that if tissue-type plasminogen activator (t-PA) is packaged in a "shear-activated nanotherapeutic" (SA-NT) particle, local blood-flow profiles can distribute the drug to where it is needed most. The results of their study involving mouse models of acute arterial thrombosis and pulmonary embolism suggest that the total administered dose can be reduced by a factor of approximately 100, as compared with intravenously delivered t-PA. The potential benefits associated with this approach are faster reperfusion, lower risk of hemorrhage, and earlier initiation of fibrinolytic therapy, possibly by first responders.

The idea that fluid forces and, in particular, shear stress (the tangential force per unit of area exerted by the flowing blood) can modulate the rate of clot dissolution is not new. Approaches that use parallel-plate flow chambers and perfusion of either human whole blood or plasma containing a fibrinolytic drug over preformed mural fibrin clots have already shown that the rate of clot dissolution is enhanced at higher shear stress. This enhancement is due to increased transfer and replenishment of the drug on the front surface of a clot, permeation through the fibrin mesh of the clot, and mechanical tearing of its three-dimensional structure.[2] Given the tremendous clinical benefits and considerable risks associated with fibrinolytic drugs, continued reevaluation of the relationship between flow and clot dissolution is warranted. Korin and colleagues have leveraged the unique features of the stenotic flow field to good effect.

SA-NTs are platelet-sized aggregates that self-assemble from hydrophobic nanoparticles, which have an average diameter of 200 nm. Experiments with the use of a rheometer and microfluidic chambers show that SA-NTs are stable under normal arterial shear stress but disaggregate at the high shear stresses that are typical of arterial stenoses. The surface of the nanoparticles is coated with t-PA to render the particles biochemically active; the t-PA is bound by surface conjugation with the use of streptavidin–biotin. With this new design, SA-NTs sequester most of the t-PA dose as they pass through normal vasculature, but when they encounter pathologically high shear stress, they break into nanoparticles that expose the t-PA dose locally. High shear stress ($\geq$100 dyn $\cdot$ cm^{-2}) occurs at the apex of any clinically significant arterial stenosis, so the use of SA-NTs releases t-PA just where it is needed most, along the apex and just downstream of the stenosis, allowing the t-PA to bind to a growing thrombus or ulcerated atheroma (Fig. 1). Another localizing feature exploits the fluid mechanics of particle drag: because of their larger diameter, intact SA-NTs have high drag forces that prevent binding to mural clots, whereas the nanoparticles released by high shear stress are subject to much lower drag forces, allowing them to bind to fibrin. SA-NT concentration should also be enriched near the vessel wall (an effect called "margination") because of erythrocyte motion and deformability under arterial shear stresses.[3] In the study by Korin and colleagues, the experimental control groups included coated but nonaggregated nanoparticles, which were about as effective as soluble t-PA; this shows that shear activation is critical to the success of SA-NTs.

There is plenty of research ahead before the clinical value of SA-NTs can be known, including research on clearance mechanisms and pharmacokinetics and testing in humans. Fortunately, the major constituents, polylactic-co-glycolic acid

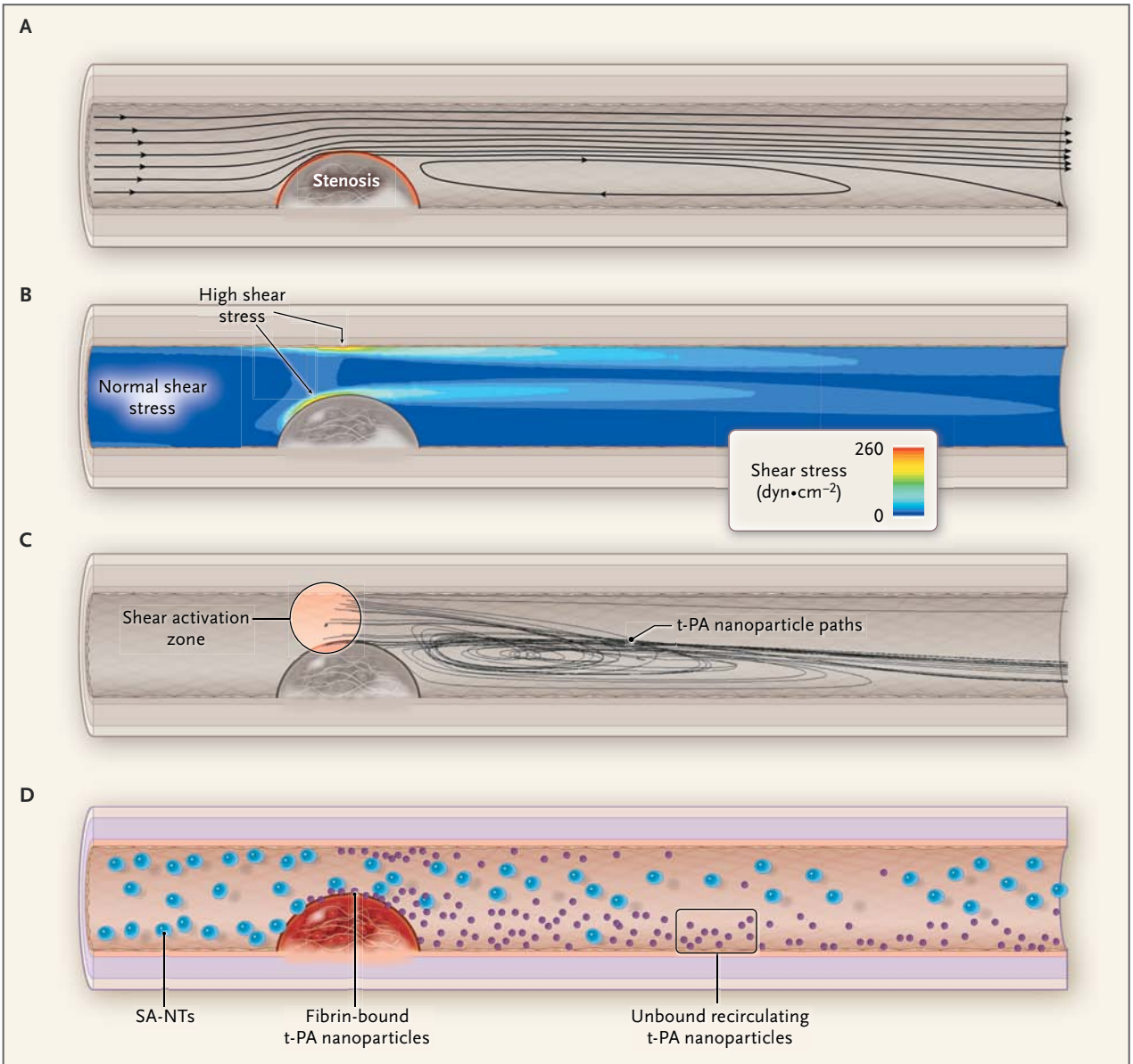

Figure 1. Leveraging Flow Features of Stenosis.

Korin et al.[1] recently described how shear-activated nanotherapeutic (SA-NT)–induced fibrinolysis can be achieved by leveraging the flow features of an arterial stenosis. Panel A shows the stenosis due to a partially occlusive thrombus, atheroma, or both. Flow streamlines are constricted along the stenosis surface, leading to high flow velocity and velocity gradients near the apex of the stenosis and slower recirculating flow behind the stenosis. Panel B shows that fluid shear stress (shown in a cross section of a blood vessel) is normal upstream of the stenosis (10 to 20 dyn•cm^{-2}), increasing to pathologically high stress (>100 dyn•cm^{-2}) near the artery wall at the apex of the stenosis. Panel C shows a three-dimensional view of the region of shear activation and the released nanoparticle flow paths from the high shear-stress zone; unbound nanoparticles are swept into the poststenotic recirculation zone. Panel D shows platelet-sized SA-NTs that stay intact and expose minimal t-PA under normal arterial shear stresses but break down because of high shear stress near the stenosis surface, releasing high concentrations of t-PA–coated nanoparticles that can adhere to fibrin in a thrombus, activate plasminogen to plasmin, and dissolve the thrombus. The recirculation zone (to the right of the stenosis shown in Panel A) also brings unbound t-PA nanoparticles back to the downstream face of the stenosis. In normal arterial flow past a mural nonocclusive clot (not shown), shear stress is less than 100 dyn•cm^{-2} and no shear activation occurs.

and t-PA, are approved with long clinical histories, but the chemicals used for nanoparticle–t-PA conjugation (biotin and streptavidin) could cause an immune response. Data are also lacking on the risk of hemorrhage. It is well accepted that hemodynamics also regulate the rate of hemostasis and the type of clot formed: platelets are activated and aggregate in flowing blood when they encounter locally, even for a few milliseconds, abnormally high shear stresses.[4] This aggregation is independent of fibrinogen and, thus, the t-PA–coated SA-NTs are not expected to have an effect on platelets in this context. Furthermore, the molecular mechanisms of platelet adhesion to the injured vessel wall and aggregation vary depending on the local shear stress; low flow results in the formation of fibrin-rich thrombi, whereas arterial flow generates platelet-rich thrombi.[5] When administered simultaneously with injury to an arterial wall, the SA-NTs significantly delayed the time to occlusion as compared with non–SA-NTs (which are either dispersed prior to injection into the bloodstream or fused with heat and unable to disperse under high flow),[1] probably because, after shear-dependent breakup, the SA-NTs achieved the highest concentration of drug on the developing thrombus. However, arterial (platelet-rich) thrombi become resistant to lysis with time after formation because of platelet-induced clot retraction and plasminogen-activator inhibitor. The efficiency of the t-PA–coated SA-NTs decreased significantly with time after an arterial thrombus was formed[1]; this confirms the critical time window within which fibrinolytic drugs need to be administered to be most effective.

The recent findings on SA-NTs will almost certainly motivate biomedical engineers to develop new SA-NT agents. Two goals are the development of prophylactic antithrombotic or fibrinolytic SA-NTs devised to stay in circulation for days or weeks in patients at high risk for thrombosis, and shear-activated antiproliferative or antiinflammatory SA-NTs to slow or reverse the growth of atherosclerotic lesions.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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