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Shear targeted drug delivery to stenotic blood vessels

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ABSTRACT

In this review we focus on shear targeted drug delivery as a novel strategy to selectively deliver drugs to sites of vascular obstruction. We review the physics of stenotic (abnormally narrowed) blood vessels, while focusing mainly on the hemodynamics and transport phenomena at these sites. We then discuss how the local abnormal levels of shear stress, which can mechanically activate platelets, can be leveraged for localized drug delivery. We describe the development of Shear Activated Nano-particle Aggregates (SA-NPAs) that are designed to release and localize their nanoparticle drug carriers at sites of vascular stenosis. We present results in a variety of *in vivo* models, demonstrating the superiority of SA-NPAs carrying a thrombolytic drug compared to conventional treatment with the free drug. We also describe, shear-stress sensitive lenticular liposomes, which also show selective release under stenotic flow conditions. We then discuss limitations of both technologies, challenges in this new field and potential future applications. Altogether, we believe that mechano-sensitive therapeutics may offer a potential new approach for treatment of cardiovascular diseases.

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1. Introduction

Obstruction of blood flow, which may result in deadly outcomes, is a known feature of a variety of common cardiovascular diseases (CVD) including acute myocardial infraction, stroke, peripheral artery disease and pulmonary embolism among others. Despite clinical advancements over the last decades, including the introduction of stenting procedures, one out of three deaths in North America are attributed to CVDs (Lloyd-Jones et al., 2010). Thus there is need for new, better therapeutics for the treatment of CVDs. Targeted drug delivery may offer improved therapeutic to sites of vascular disease by concentrating the drugs drug at the required site, thus increasing their efficacy and reducing possible side effects (Langer, 1998). Most drug targeting approaches utilize abnormal bio-chemical features of diseased tissues, such as abnormal pH or upregulated cell surface molecules (Petros and DeSimone, 2010; Torchilin, 2000). Here, we review a new physical based approach for targeted drug delivery to stenotic blood vessels that recapitalizes on the abnormal hemodynamics at these sites. We then discuss limitations of current technologies for shear drug delivery, challenges in this new field and potential future applications.

2. Hemodynamics and transport phenomena in stenotic blood vessels

Stenotic blood vessels, characterized by a locally constricted segment, are known for their abnormal hemodynamics which have been shown to play a dominant role in disease progression. From a fluid mechanics point of view, the locally constricted region induces a Venturi effect on the flow. Thus a low pressure zone is formed at the narrowed section of the blood vessel (P_2 in Fig. 1A) and a high pressure region appears downstream of the constriction, where the vessel widens again (P_3 in Fig. 1A). These changes are well described by the Bernoulli law for laminar flows (Eq. (1)):

$$\Delta P = -\frac{\rho Q}{2}\left[\left(\frac{1}{A_2}\right)^2 - \left(\frac{1}{A_1}\right)^2\right] \rightarrow P_2 = P_1 - \frac{\rho Q}{2}\left[\left(\frac{1}{A_2}\right)^2 - \left(\frac{1}{A_1}\right)^2\right] \quad (1)$$

Where ΔP is the pressure difference ($P_2 - P_1$), ρ is the fluid density, Q is flow rate and A_1 and A_2 the cross-section areas. As the stenosis increases (A_2 decreases) the pressure difference increases and more importantly P_2 decreases. As fluids always flows from high pressure to low pressure, under the described flow conditions at the stenosis region, the boundary layer may separate and fold in on itself inducing a recirculating flow (Chang, 2014) (Fig. 1A). This recirculating flow, in coronary arteries, generally appears immediately after peak systole and disappears during the systolic acceleration which superposes a positive pressure gradient on the flow thus reducing flow separation (Chang, 2014). The flow diversion and the folding of streamlines create transient high shear flows with increased wall shear stress

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(WSS) at the apex of the narrowing and prior to it. This high shear region, is followed by a low wall shear region at the recirculating flow zone downstream of the constriction (Ku et al., 1985). Fig. 1B shows a qualitative map of strain rate around a stenotic blood vessel showing the high strain region around the apex of the stenosis and the low shear, recirculating flow region. The low shear, disturbed flow zone has been shown to induce endothelial dysfunction and to correlate with progression of plaque growth (Chiu and Chien, 2011; Davies, 2008; Wentzel et al., 2012). While, the high shear region, on the other hand, has been shown to induce platelet activation thus contributing to athero-thrombotic complications.

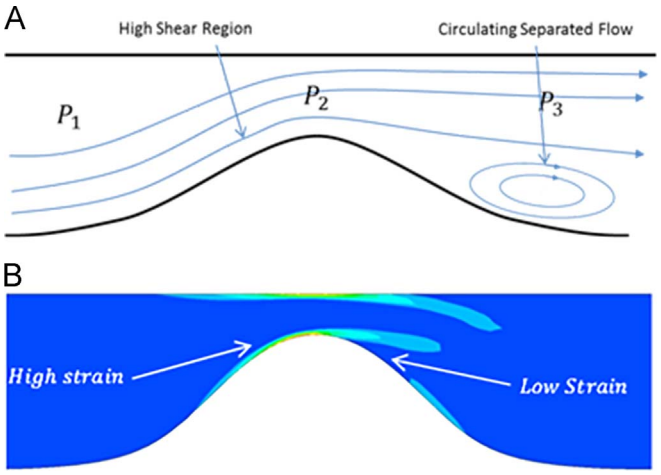

Fig. 1. A) Illustration of the streamlines in a stenosed blood vessel. P_1 is the inlet pressure, P_2 is the pressure at the minimum cross-section of the blood vessel and P_3 is the pressure downstream of the constriction. B) Qualitative representation of the strain rate distribution at site of blood vessel stenosis.

3. Platelet shear activation

Platelets play a key role in the normal maintenance of homeostasis and thrombosis. Upon activation, platelet secrete procoagulant and self-stimulating factors, adhere to surfaces and aggregate (Davì and Patrono, 2007). In addition to activation by biochemical factors, platelets can mechanically activate by high hemodynamic shear stress (Raz et al., 2007). In order for platelet shear activation to occur, platelets must not only be exposed to abnormally high levels of shear stress but also need to experience the elevated shear for a sufficient amount of time. Thus the platelet shear activation level (*AL*) is a function of its recent history of exposure to shear stress. From a Lagrangian point of view the activation level (*AL*) can be thus defined as the integral of the above product as show in Eq. (2):

$$AL = \int \tau dt \tag{2}$$

where t the local residence time is τ is the local shear stress

Local narrowing in blood vessels provides both high shear and low shear regions making them prone to thrombus formation. Fig. 2A describes the local particulate dynamics of blood flow at stenotic sites. Platelets and white blood cells (WBCs) traveling near the endothelium are exposed to high shear existing near the walls. Additionally, the flows near the wall are slow boundary layer flows (Schlichting and Gersten, 2003) thus allowing platelets a sufficient exposure time required for their activation. Immediately downstream of the stenosis, the flow decelerates and platelets may collide and aggregate thus promoting thrombus formation (Ku et al., 1985). As the stenosis progresses, all these effects become more dominant and correspondingly the risk of thromboembolic complications increases.

In this review we focus on shear targeted drug delivery, illustrating how the above described physical conditions, which govern platelet activation at stenotic regions, can also be potentially used to develop a drug delivery system that utilizes these conditions to selectively deliver drugs to sites of vascular disease.

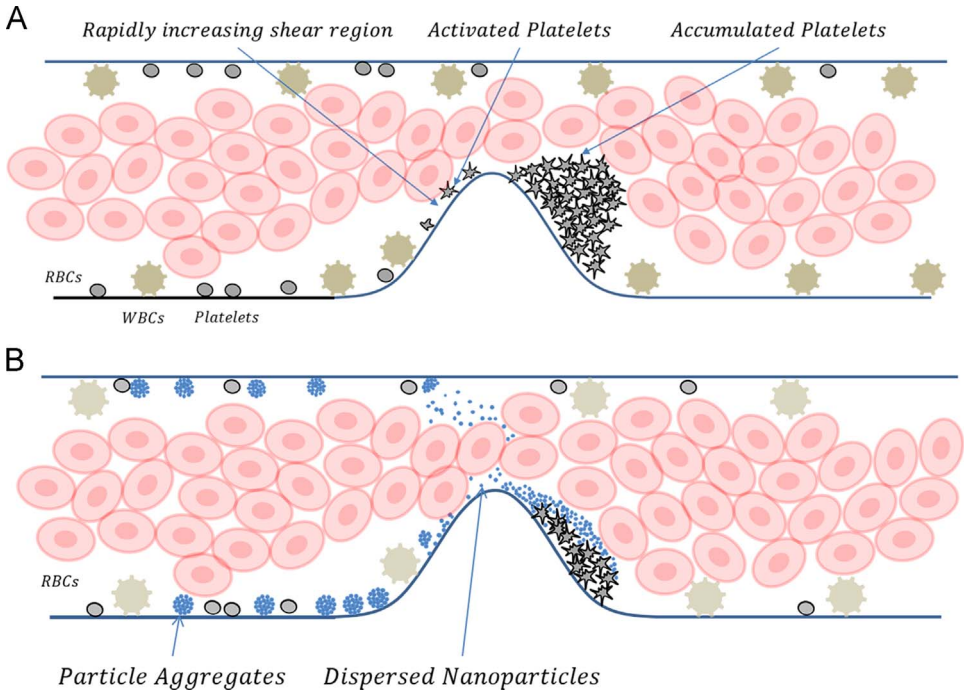

Fig. 2. A) An illustration of platelet shear activation when flowing through a vascular stenosis. The platelets activate at the high shear zone, and then aggregate at the site of stenosis downstream of the narrowing. B) An illustration of SA-NPAs shear activation when flowing through a vascular stenosis. The SA-NPAs disperse into their nanoparticle drug carriers at the high shear zone, which adhere and localize at the site of stenosis downstream of the narrowing.

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