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A Hydrodynamics based Proposal to Substitute Heparin by Drag Reducing Polymers

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Abstract

Blood exhibits a non-Newtonian rheology, i.e., its shear-rate to shear-stress relationship is non-linear, i.e., one has to apply a threshold force, the so-called yield-stress before it moves at all. This particularity is due to the composition of blood and the particular qualities of its components (Boron et al., 2005). For our purpose we will consider that blood consists mainly of plasma with near-Newtonian flow properties and red blood cells (RBC) thus leading to a two-phase flow behavior where the plasma acts as the carrier phase and the RBC as suspended therein liquid-drop-like carried phase (Pinkowski, Lilienblum, 2015). At low shear rates (low velocity gradients) RBC tend to form rouleaux structures and these primary, randomly scattered rouleaux tend also to group together to form secondary rouleaux structures (Kulicke, 1986). Fibrinogen adhered to the vessel wall forms together with these secondary rouleaux fibrinogen filaments leading to increased viscosity at low shear rates. These fibrinogen filaments can be considered as precursors of blood clots. The key component in hemostasis is an elongated glycoprotein in the plasma that through activation by thrombin self-assembles into a first fibrin clot (Brown, J.H. et al. 2000).

Index terms—

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Heparin by Drag Reducing Polymers I. Introduction lood exhibits a non-Newtonian rheology, i.e., its shear-rate to shear-stress relationship is nonlinear, i.e., one has to apply a threshold force, the so-called yield-stress before it moves at all. This particularity is due to the composition of blood and the particular qualities of its components (Boron et al., 2005). For our purpose we will consider that blood consists mainly of plasma with near-Newtonian flow properties and red blood cells (RBC) thus leading to a two-phase flow behavior where the plasma acts as the carrier phase and the RBC as suspended therein liquiddrop-like carried phase (Pinkowski, Lilienblum, 2015). At low shear rates (low velocity gradients) RBC tend to form rouleaux structures and these primary, randomly scattered rouleaux tend also to group together to form secondary rouleaux structures (Kulicke, 1986). Fibrinogen adhered to the vessel wall forms together with these secondary rouleaux fibrinogen filaments leading to increased viscosity at low shear rates. These fibrinogen filaments can be considered as precursors of blood clots. The key component in hemostasis is an elongated glycoprotein in the plasma that through activation by thrombin self-assembles into a first fibrin clot (Brown, J.H. et al. 2000).

Heparin is used to treat and prevent blood clots in the veins, arteries, or lung, like venous thrombosis, pulmonary embolisms, coagulopathies and coronary artery clots. It is used also before surgery to reduce the risk of blood clots. Common side effects of heparin, however, are easy bleeding and bruising. Patients with renal failure have an increased risk of bleeding (Levine et al., 2001). Therefore it seems to be worthwhile to speculate about a possible replacement of heparin by another blood-thinning drug without the drawbacks of heparin mentioned.

Although it is commonly assumed that heparin produces its anticoagulent effect by inactivating thrombin and activated factor X through an antithrombin-dependent mechanism, a deeper knowledge of this noncoagulant action is considered still as very limited (Drewlo, 2013). However, from an hydrodynamic point of view the

systemic (intravenous) administration of heparin will reduce the blood viscosity (Chandran, 2007). In other words the blood-thinning action of heparin consists also in facilitating the displacement of red blood cells (RBC) and inhibiting their clumping. This way the typically non-Newtonian flow pattern of blood becomes more Newtonian-like, i.e., more laminar. Hence the lower coagulation tendency due to heparin results in a better flowability of blood. At this pont it is important to point out that this better flowability tendency is valid also at rest of the blood flow, i.e., during the coagulation process. This means in turn that the coagulation process of any wound injury will slow down, i. e., heparin will deteriorate wound healing.

As was shown in detail in a previous publication (Pinkowski, Lilienblum, 2015) drag reducing polymers (DRP) in nanomolecular concentrations are capable to achieve the same effect of better flowability, i.e., they can smooth out local micro-turbulences and this way laminarize blood flow. However, it is crucial to stress at this point that this laminarizing effect of DRP vanishes at rest, i.e., the coagulation process will not slow down contrary to the action of heparin. Systemic administration of DRP into the blood circulation system have a great medical potential as was proved in vivo for many provoked lethal deseases. It was shown e.g. to be effective against atherosclerosis (Faruqui et al., 1987), and against provoked lethal hemorrhagic-shock in rats (Macias et al., 2004;Kameneva et al., 2004).

DRP injection was proposed as a novel hydrodynamic approach for the tratment of coronary artery disease (Pacella et al., 2006). Among the different polymers used for drag reduction the FDA approved water soluble polyethylene glycol (PEG) is clearly the favorite. It is also used as antifoaming agent in food (US Government, 2011). Its INS number is 1521 in the USA and E1521 in the EU resp. (Codex Alimentarius, 2012). The international nonproprietary name for PEG used in medicine is Macrogol.

Depending on the actual Reynolds numbers (Re) on distinguishes in blood rheology four different flow pattern: At high Re -turbulent flow (where the normally parabolic velocity profile becomes blunted), at medium Re -laminarity, at low Re -RBC-rouleaux, and at very low Re -the Fåhraeus-Lindqvist region (Fåhraeus-Lindqvist, 1931): in small vessels between 10 and 300 micrometers, the viscosity decreases with decreasing tube diameter due to accumulation of RBC in the vessel center. This tendency of RBC accumulation in the vessel center leaving the plasma in the vessel wall region RBC depleted is also referred to as plasma skimming (Boron et al., 2005).

In turbulent flow the mass transfer is considerably enhanced and this is true also for local microturbulences in small vessels and at low blood flow velocity as was shown previously (Pinkowski, Lilienblum, 2015). Any blood agitation and increase in blood flowability however is counteracting the coagulation process. Despite the decreased Re numbers in small vessels the decreased blood flow favors RBC aggregation which in turn is a source of local vortices with enhanced mass transfer. Systemic administration of DRP inverses the flow situation thus favoring the anticoagulation. DRP act however only during flow which that at rest the normal coagulation capacity of a patient will not be altered.

Due to the hypothetical character of the present proposal verification by animal models before any clinical trial are mandatory.

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