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The Effect of Urokinase Infusion Regimens on Thrombolysis - a Numerical Study

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Abstract

Numerical analysis was performed on the enzyme transport and the flow fields in order to predict the effectiveness of urokinase injection regimens in clot dissolution. The species and momentum transport equations were numerically solved for the case of uniform perfusion of enzyme into a fibrin clot for an arterial thrombus and a deep vein thrombus models. In order to predict the thrombus lysis efficiency of continuous and forced intermittent injections, enzyme perfusion and clot lysis were simulated for the different injection velocities. Intermittent injection showed faster clot lysis compared to continuous perfusion, and lysis efficiency was increased as injection velocity increased.

Key words : thrombolysis, enzyme transport, numerical methods, injection regimen

I. INTRODUCTION

When a blood clot is formed inside of a blood vessel, it blocks distal blood supply and causes ischemia of tissues and organs. Plasminogen activators (PAs) are delivered either intravenously or via an intravascular catheter to dissolve a blood clot. Because of the risk of systematic bleeding [1], local administration of PAs via a catheter has been recommended. In order to accelerate thrombolytic process, various delivery schemes, such as intrathrombotic injection [2], pulse jet spraying [3] and ultrasound applications [4], have been applied. These techniques have been developed to increase the penetration of enzyme into a blood clot and the active interface area of a clot, since these are the major limiting factors in rapid blood clot lysis.

Transport of PA into a thrombus is the important determinant of thrombolytic therapy because clot dissolution is limited to the regions where the PA is available. Penetration of PA into a clot is mediated by two transport mechanism, diffusion and convection. Convective transport of PA is more effective transport mechanism, and the pressure gradient determines the convective transport and thrombolysis. Blinc et al [5,6] demonstrated that lysis of a whole blood clot was faster by one or two orders of magnitude with pressure driven permeation compared to the rate where transport was limited to diffusion alone. They also showed marked increase in clot lysis under the pressure gradient of 3 kPa. Wu et al [7] reported that the velocity of the lysis front was 12 to 25-fold faster than that measured without pressure driven permeation. Diamond and Anand [8] also showed greatly enhanced lysis at the pressure gradients of 1, 10, 50 mmHg/cm. Since transport of PA into a clot is the major determinant of effective thrombolytic process, prediction of PA transportation and fibrinolytic process would be important in determining thrombolysis regimen.

Various PA administration regimens have been tried in order to achieve fast and effective lysis of a blood clot. Continuous and intermittent infusion of small volumes of highly concentrated enzyme using a transluminal catheter could increase the lysis of a blood clot. The blood clot in an artery is generally short and soft, and it can be relatively dissolved well. But, the time window for clot dissolution is small (within a few hours) because prolonged blockage of blood supply causes severe damages on the tissues of important organs. The thrombus formed inside a deep vein is hard to dissolve because of high fibrin densities and less fluid contents. Also deep vein thrombus (DVT) is long (a few to tens of centimeters). Because it is hard to transport PA inside of a relatively long thrombus by diffusion, intra-thrombus infusion of PA via a multi side-hole catheter has been used [9]. High speed injection of PA would promote enzyme perfusion by increasing the clot surface pressure, but it causes blood volume overloading and

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high systemic enzyme concentration. Intermittent injection regimens have been attempted, but their effectiveness is controversial [10].

Diamond and Anand [8] analyzed fibrin clot dissolution using multi component equations with reaction kinetics and predicted the lysis fronts moving cross a fibrin clot of various densities by solving convection diffusion equations. Their models were adequate for predicting thrombolysis under uniform perfusion of enzyme, but had limitations in calculating species transport coupled with complicated flow fields. We would like to predict the effectiveness of continuous and intermittent infusion on clot lysis by solving three dimensional flow and species equations.

II. METHODS

A. Mathematical Modeling of Thrombolysis

Thrombus dissolving process involved various enzymes and their reaction kinetics in fluid and solid fibrin phases. And the reaction kinetics required various kinetic constants which were difficult to be determined. Therefore solving all the species equations coupled with three dimensional flow fields required formidable works. In this study, one PA transport equation was solved with the momentum equations, and clot lysis was determined from PA transportation. We selected urokinase (uPA) as a plasminogen activator, and assumed that uPA transport into a clot was the rate limiting process in thrombolytic reactions. Instead of microscopic modeling of fibrin fiber dissolution and solving reaction kinetics equations, a clot was modeled as an isotropic porous medium, which is treated as a momentum sink in numerical calculation procedures. Once uPA was transported into a clot, it dissolved the clot and the interface between the fluid and the porous zone moved forward as fibrinolysis proceeded. We assumed that clot lysis occurred for the porous regions where PA was perfused within five to twenty minutes. Clot lysis followed PA perfusion after a lag time of 13±4 min because of the time required for enzymatic processes [11]. Quasi-steady state was assumed for dissolving process. During a time interval of 5 to 20 minutes, unsteady uPA transport and momentum equations were solved. At the end of time interval, the clot regions where uPA was perfused were changed to fluid region, generating a new interface of the fluid and the porous zone. Although the time interval seemed to be long, the perfused distance into a clot was usually less than 1 mm during the time interval.

Unsteady species transport equation was simultaneously solved with continuity and three dimensional momentum equations. Flow fields were assumed to be incompressible laminar Newtonian flow. Calculation domains were discretized, and the governing equations were solved by a computational fluid dynamics software package (Fluent 6.2) which was based on the finite volume formulation. Segregated implicit solver was used. First order upwind scheme was used for spatial discretization, and SIMPLE/PISO scheme was used for pressure and velocity coupling. The validity of our lysis modeling and numerical schemes had been verified [12] by comparing our calculated results of clot lysis with the in vitro experimental data of Wu et al [7].

B. Arterial Thrombus and Deep Vein Thrombus Model

Arterial thrombus (AT) model and deep vein thrombus (DVT) model were simulated. In an arterial thrombus model, urokinase was injected onto the clot surface via a hole at the end tip of a catheter. The diameter of a blood vessel was 3 mm, and the length of a clot was 5 mm. A 2 mm diameter catheter with a 0.5 mm diameter end-hole at the tip was located coaxially with the vessel, and enzyme was ejecting at a given velocity and impinging on the clot surface normally. This model was composed of 92,000 hexahedral cells. Finer grids were used near the nozzle exit.

In a DVT model, a catheter with side holes was inserted into a thrombus, and urokinase was injected radially inside of a thrombus. We considered a 70 mm long thrombus formed inside of a vein (diameter of 13 mm). An intra-thrombus catheter (diameter of 1.6 mm), which had 14 side holes (diameter of 0.89 mm) spirally located along the axis, was inserted into a thrombus. Since the geometry was repeated periodically along the axis, a 5 mm portion of a thrombus with one ejecting hole was modeled for numerical analysis.

The cylindrical blood vessel was filled with plasma, and the blood clot was modeled as porous media with the specific permeability of 10-10 to 10-11 cm2 and high porosity (>0.9) [13]. Spatial variability of a porous zone was neglected, and isotropy was assumed. Porous media was modeled as a momentum sink. In the fluid zone, unsteady momentum and species equations were solved. One species equation represented uPA (molecular weight of 54,000) transport in plasma. Diffusivity was set to 5x10-7cm2/s, which is the typical protein diffusivity in the water phase of the gel [14]. The first order implicit scheme was used for unsteady calculations. Time step size was 10 to 30 seconds, and the solution converges within 20 iterations per time step. In solving forced infusion case, smaller time step (0.1 second) was used during the injection period. Unsteady transport equation was solved for a given time interval (about 5 minutes), and then the porous region where uPA permeated was assumed to be completely dissolved. Each 5 minute time interval represented the time required for enzymatic lytic process. Velocity

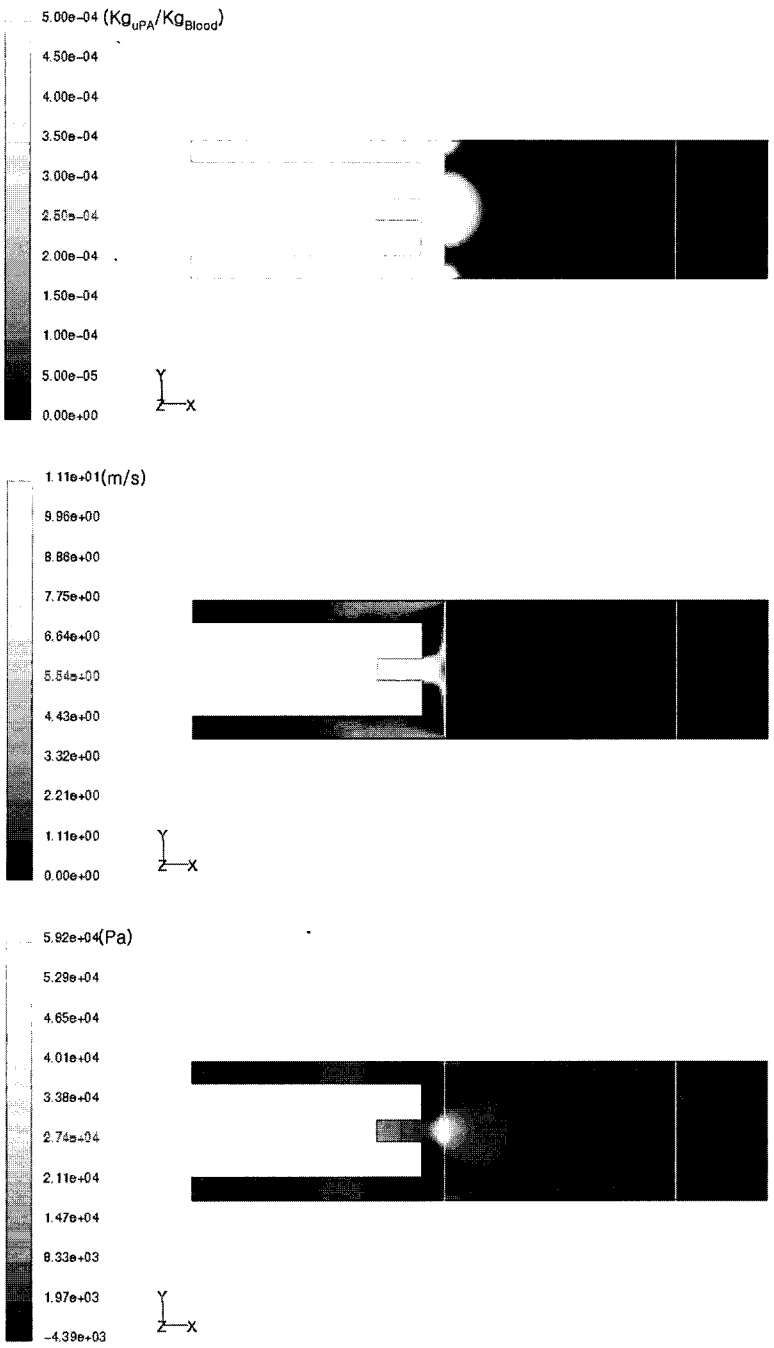

Fig. 1. Contour of concentration, velocity and pressure in the symmetry plane of a vessel at the end of the initial pulsed injection of enzyme at 10 m/sec. (AT Model)

boundary condition was given at the nozzle, and pressure outlet boundary conditions were used for the outlets. Constant species concentration was given for inlet boundary conditions for a species equation.

III. RESULTS

In order to predict the effectiveness of thrombolysis protocols, the effects of administration methods - continuous infusion and intermittent injection, and enzyme injection velocity on thrombolysis were explored. Since the administration of highly concentrated enzyme would accelerate the lysis in transcatheter enzyme delivery [15], 10 μM urokinase solution was injected via a catheter. In continuous infusion, the flow rate was 1 ml/min in the AT model and 5 ml/min in the DVT model. In order to study the effect of injection velocity, the

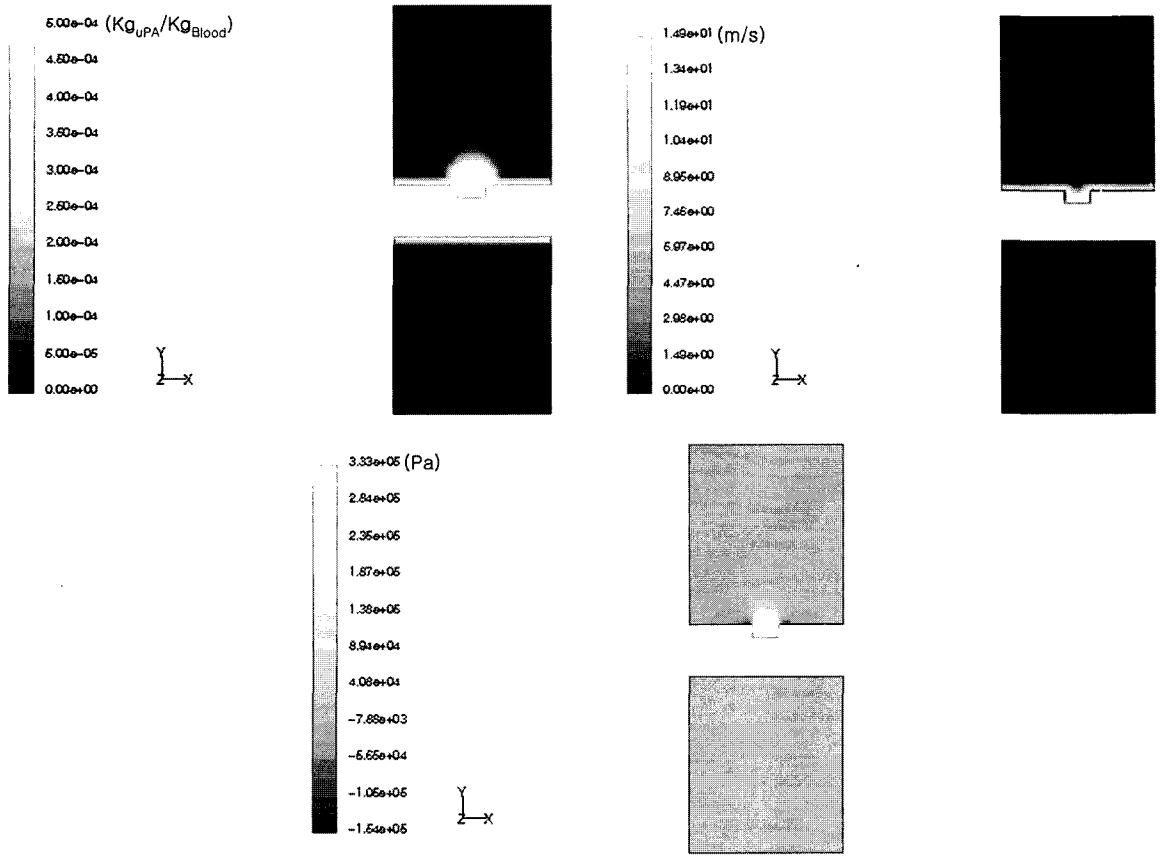

Fig. 2. Contour of concentration, velocity and pressure in the symmetry plane of a vessel at the end of the initial pulsed injection of enzyme at 10 m/sec. (DVT Model)

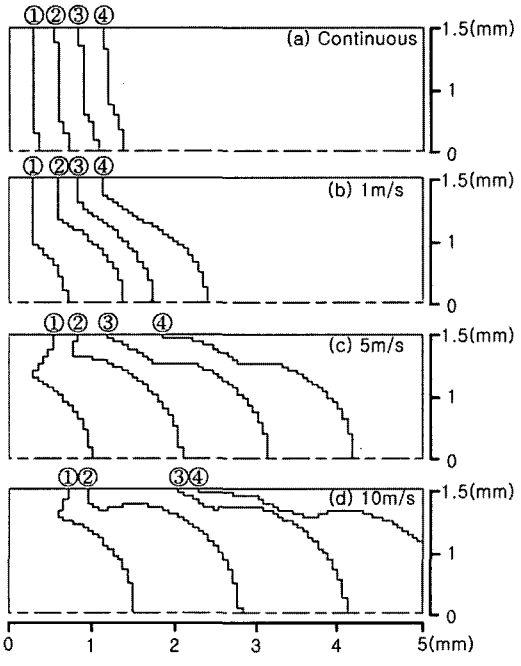

Fig. 3. The lysis front positions in the symmetry plane of the vessel for continuous perfusion and intermittent injections (AT Model). Symbol ①, ②, ③, ④ denotes the time at 5, 10, 15, 20 minutes.

enzyme was injected at velocity of 1, 5 and 10 m/sec periodically in every 5 minute. Higher injection velocity accompanied overdose of enzyme solution, which caused blood volume overloading and hemorrhage. The duration of forced injection was determined so that infusion volume during five minutes was the same for continuous infusion and intermittent injections. The injection durations were 25, 5 and 2.5 seconds for the injection velocity of 1, 5 and 10 m/sec. The concentration, velocity and pressure contours in the AT and the DVT model at five minutes after initial injection at 10 m/sec are shown in Fig. 1 and Fig. 2. High speed jet impinged on the clot surface and moved in retrograde (AT model) and radial (DVT model) direction. The pressure at the clot surface had the maximum value at the stagnation point, and decreased inside the clot. Higher pressure region in the porous clot had higher uPA concentration. The lysis front positions in continuous perfusion and intermittent injections in AT the model are shown in Fig. 3. Continuous perfusion dissolved the clot uniformly while forced injection dissolved the central region further, where the enzyme jet impinged. Fig. 4 shows the lysis front positions in continuous perfusion and intermittent injections in the DVT model. The upper panel

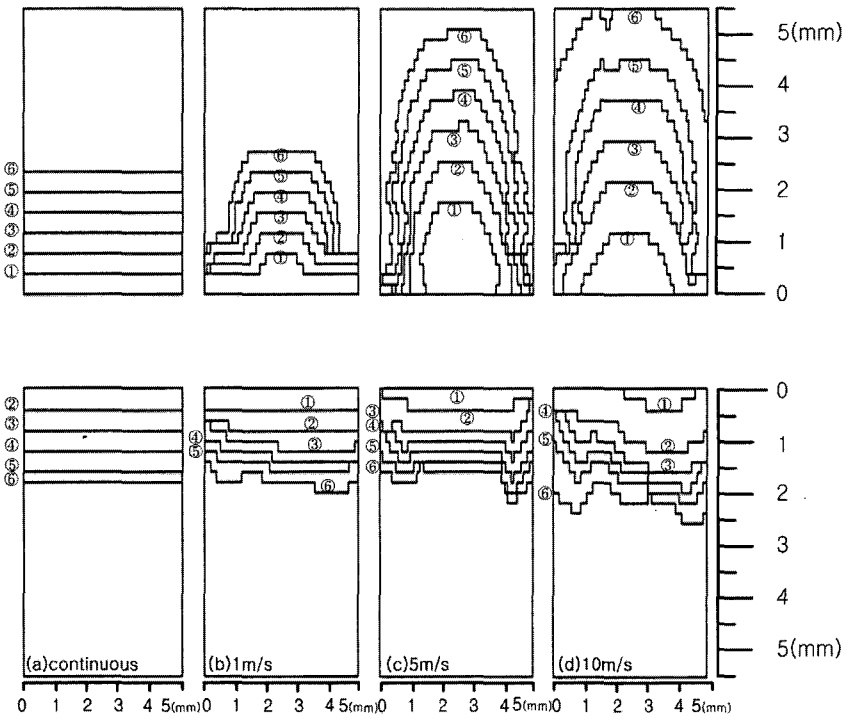

Fig. 4. The lysis side positions in the symmetry plane of the vessel for continuous perfusion and intermittent injections (DVT Model). Symbol ①, ②, ③, ④, ⑤, ⑥ denotes the time at 5, 10, 15, 20, 25, 30 minutes.

which represents ejection-hole side showed faster clot lysis compared to the lower panel. The clot lysed faster in the ejection-hole side as the injection velocity increased, but there were no significant effects of ejection velocities in the opposite side. In order to quantify clot lysis effectiveness, the dissolved volumes were integrated and divided by original clot volume. The percent volumes lysed (the ratio of dissolved clot volume to original clot volume) were calculated for the different injection velocities in the AT and the DVT model

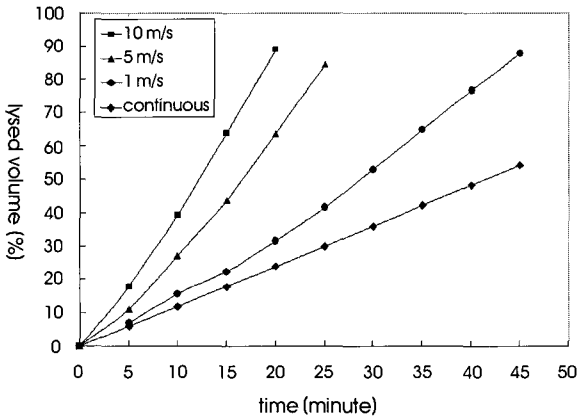

Fig. 5. The percent clot volumes lysed for continuous infusion and intermittent injections with the period of five minutes for different injection velocities for the AT model.

(Fig. 5 and Fig. 6). In the arterial thrombus model, intermittent injection accelerated clot lysis compared to continuous infusion, and its effectiveness was enhanced as the velocity increased. In the DVT model, intermittent injection with 1 m/s did not show enhanced clot lysis compared to continuous infusion, but intermittent injection with higher speed showed effective clot lysis. Localized uPA transport near the impingement region might be responsible for slow clot lysis in the DVT model when ejection velocity was small (1 m/sec). The percent clot volumes lysed were smaller in the DVT model compared to those in the arterial thrombus model at a given time, but the actual lysed clot volumes were greater in the DVT model. The initial clot volume in the DVT model was more than 40 times greater than that in the arterial model.

Ⅳ. DISCUSSIONS

The rate limiting step in thrombolysis is the transport of enzyme into a clot, and thrombolytic process is mainly modulated by pressure induced permeation. The pressure gradient determines the permeation velocity by Darcy' law, and fast enzyme permeation augments clot dissolution. In clinical application of thrombolytic therapy, it is not easy to increase the clot surface pressure even though increasing intraluminal pressure by occlusion balloons has been

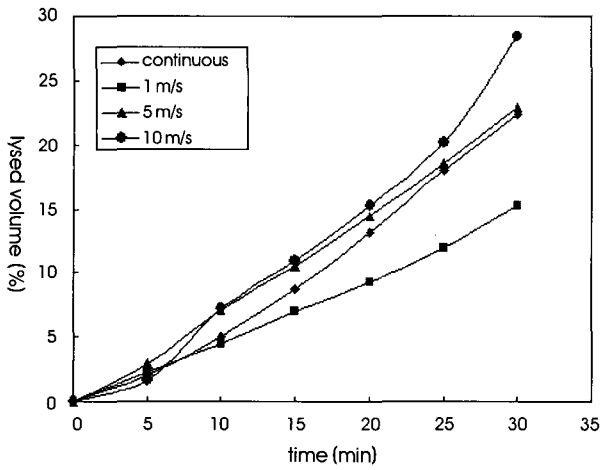

Fig. 6. The percent clot volumes lysed for continuous infusion and intermittent injections with the period of five minutes for different injection velocities for the lysis side position for the DVT.

attempted [16]. The clot surface pressure can be increased by directly injecting enzyme with high speed. The kinetic energy of ejecting jet is converted to the stagnation pressure on the clot surface, which augments enzyme perfusion into a clot. Higher velocity augments enzyme transport, but the injection velocity should be limited. High speed injection usually increases infusion flow rate, and excessive enzyme solution administration causes blood volume overloading and hemorrhagic complications. Also fast infusion may reduce the local retention of an enzyme because of fast moving retrograding flow of injectate. It has been shown that the slow administration of concentrated enzyme would accelerate the lysis of thrombi in vivo [17]. Forced intermittent injection would enhance enzyme permeation without increasing the infusion enzyme volume by decreasing the injection duration.

Our results showed that the intermittent infusion enhanced clot lysis compared to the continuous infusion while delivering the same amount of enzyme. In continuous infusion, enzyme was transported into a clot mainly by diffusion while additional permeation by forced ejection facilitated enzyme transport into a clot. Clot lysis was accelerated as the ejection velocity increased. Because stagnation pressure on the clot surface was proportional to the square of ejection velocity, and higher ejection velocity enhanced enzyme permeation. As the clot dissolved, the shape of lysis front deformed less uniformly and the effective clot surface area became larger in the forced injection compared to the continuous infusion. Therefore, both high clot surface pressure and large interface area would promote enzyme transport into a clot. As the injection velocity increases, clot lysis was accelerated except for the case of low velocity injection in the DVT model. Intermittent injection with the velocity of 1 m/sec in the DVT model showed slower lysis compared to the continuous injection. The injection duration was shorter in the intermittent injection so as to infuse the same amount of the enzyme during a thrombolytic procedure. In this case, injected enzyme might not have enough time to penetrate into a clot, and targeting efficiency which was the ratio of marker content of the clot and the delivered dose would be lower. When the ejection velocity was increased, the effects of permeation enhanced clot dissolution would override those of reduced penetration time.

Transport of an enzyme into a clot is affected by flow fields -fluid motion and pressure - and clot properties. In this study, we have changed flow fields by applying different enzyme administration regimens in order to enhance the enzyme transport into a clot. The effects of flow fields on enzyme transport into a clot would be affected by clot properties. Less porous and impermeable clots, such as retracted whole blood clots, provides more resistance to perfusion [18], therefore the effects of injection velocity and frequency on enzyme perfusion may be different for various clots. Since thrombus is a very heterogeneous entity and its physical properties and compositions are diverse [19], further study should be performedin order to suggest appropriate injection parameters for the different clots. But our model study could provide some insight into the advantage of forced intermittent injection. Even though modeling a clot as a homogeneous isotropic porous media cannot reveal microscopic structures and instantaneous lysis of fibrin fibers, a species transport equation can predict enzyme transport with the proper values of porosity and permeability in the quasi-steady case. Further refinement of lysis modeling should be required to predict instantaneous clot lysis.

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