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Numerical modeling of thrombolysis - Effects of nozzle types and ejection velocities

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Abstract

Direct injection of a fibrinolytic agent to the intra-arterial thrombosis may increase the effectiveness of thrombolysis by enhancing the permeation of thrombolytic agents into the blood clot. Permeation of fibrinolytic agents into a clot is influenced by the surface pressure, which is determined by the injection velocity of fibrinolytic agents. Computational fluid dynamic methods were used in order to predict clot lysis for different jet velocities and nozzle arrangements. Firstly, thrombolysis of a clot was mathematically modeled based on the pressure and lysis front velocity relationship. Direct injection of a thrombolytic agent increased the speed of thrombolysis significantly and the effectiveness was increased as the ejecting velocity increased. The nine nozzles model showed about 20% increase of the lysed volume, and the one and seventeen nozzles models did not show significant differences. Secondly, thrombolysis was modeled based on the enzyme transport and the fluid flow equations, and quasi steady numerical analysis was performed. Clot lysis efficiency was also increased as injection velocity increased.

Key Words: thrombolysis, enzyme transport, computational fluid mechanics.

Introduction

In order to dissolve a blood clot and restore the patency of a blood vessel, various treatments have been used, such as thrombolysis using pharmacological agents, mechanical thrombectomy[1], and angioplasty using a balloon or a stent[2]. Direct or intravenous injection of thrombolytic agents, such as tissue plasminogen activator (tPA), urokinase (uPA), streptokinase (SK), have been used for the treatment of acute thrombosis. Direct injection of a drug into a clot is more effective because of efficient delivery of a drug into a clot and locally high drug concentration. Difficulties involved in direct injection method are related to the delivery of a catheter to the thrombosed blood vessel. Intravenous injection is conveniently applied to the patients, but thrombolytic efficiency is low. Pharmacological treatment is a safe and effective method, but the drawbacks are delayed clot lysis and bleeding. Rapid restoration of flow is a major advantage of thrombectomy, but increased incident of distal embolization and blood vessel damages are the disadvantages.[3] Recently, a rheolytic thrombectomy device, which generates local low pressure by Venturi effects and aspires the clots, has been used[4]. But the size of a catheter limits its applications in small size vessels. Injecting thrombolytic agents with high speed into the clot may increase the effectiveness of thrombolysis by achieving both benefits of pharmacological and mechanical means.[5,6] Direct injection of a thrombolytic agent to the thrombus increases the effectiveness of thrombolysis by enhancing the permeation of a thrombolytic agent into a blood clot. Thrombolysis is affected by the transport of pharmacological agents and the lysis kinetics. Lysis process involves various reaction cascades[7], and the reaction kinetics depends on drug types, concentrations, administration methods, and clot properties. A blood clot is very heterogeneous entity which is composed of fibrin fibers and blood cells, and its compositions, fibrin diameters, porosity and fluid contents determine lysis characteristics.[8,9] Factors related to lysis kinetics

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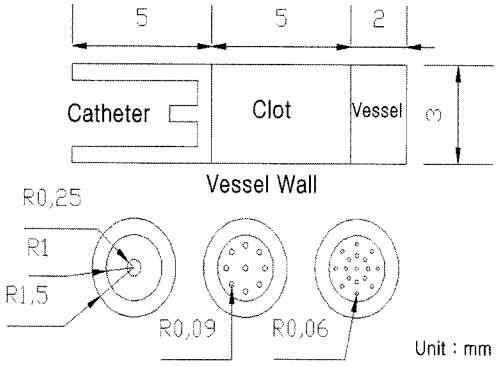


Figure 1. Schematic diagram of the calculation domain – a blood vessel, a catheter and a thrombus.

are hard to be controlled by treatment schemes, but thrombolysis can be accelerated by enhancing the transport of pharmacological agents into a clot. Transport of pharmacological agents into a clot is mediated by diffusion and permeation, but the dominant mechanism is permeation. Previous workers demonstrated that lysis of a whole blood clot was faster by one or two orders of magnitude compared to the rate where the transport was limited to diffusion alone.[10] Permeation is directly affected by the pressure gradient across the porous media, therefore the pressure on the clot surface influences the thrombolytic process. Wu *et al* [11] reported that the lysis front velocity increased as the permeation pressure increased for the fibrin and whole blood clots. Perfusion of a drug into a clot is affected by the pressure on the surface, and the injection velocity of a thrombolytic agent changes the pressure distribution. The effects of permeation pressure on the drug perfusion and thrombolysis have been studied.[11,12] Most of studies have been performed on uniform clot surface pressures applied using a static fluid column, but the effects of ejection velocity and nozzle type have not been studied. We would like to calculate clot lysis for different jet velocities and ejecting nozzle arrangements, and investigate their effects on thrombolytic process.

Methods

In order to analyze the flow fields of ejecting jets onto a clot surface, a segment of a blood vessel with a catheter was modeled. We assumed a blood vessel (diameter of 3 mm) and a catheter (diameter of 2 mm) were coaxially located, and nozzles (length of 1 mm) were attached at the end of a catheter. Three different models were considered – one nozzle (1N: diameter of 0.5 mm), nine nozzles (9N: diameter of 0.18 mm), and 17 nozzles (17N: diameter of 0.12 mm) model. In multiple nozzle models, one nozzle is located at the center and other nozzles are located radially with an equal spacing. Each model had the same total cross sectional ejection area, therefore total infusion flow rate are the same for the same ejection velocity. Since the cross section of each model is symmetric over 45 degree, one eighth of the vessel cross section is modeled. The one nozzle model and multiple nozzle models are composed of about 34,000 and 60,000 hexahedral cells, respectively. A commercial computational fluid dynamic package (Fluent 6.2) was used to calculate the flow fields. We assumed that the vessel wall was rigid, and the blood and drug were Newtonian fluid. Velocity inlet and pressure outlet boundary conditions were applied to the nozzle entrance and the annular exit area between a vessel and a catheter wall, respectively. Flow fields were calculated for three ejecting velocities – 1, 3, 5 m/sec. The higher velocity generated blood volume overloading and high mechanical stress that might cause vessel wall damage, thrombus fragmentation and emboli production.[6]

Blinc *et al* [12] showed that 2 cm blood clots could be lysed within 30 minutes by perfusing tPA under the pressure of 3 kilopascal. Wu *et al* [11] measured the velocity at which a lysis front moved across a clot (lysis front velocity) for different pressure gradients. In vitro experiments were performed for fine and coarse fibrin clots using 1 μmole of urokinase. The results showed enhancement of the lysis front velocities by increasing pressure gradients. Since the lysis front velocity increased linearly to the permeation pressure up to a few kilopascals, we could obtain a linear relationship between lysis front velocity (v: mm/min) and pressure (P: Pascal) based on the Wu *et al*'s experimental data for the fine fibrin clots.

$$v = 0.0002\,P + 0.0129$$

Considering the delay between the drug perfusion and the clot lysis, the distances lysed into clot (DL) in 5

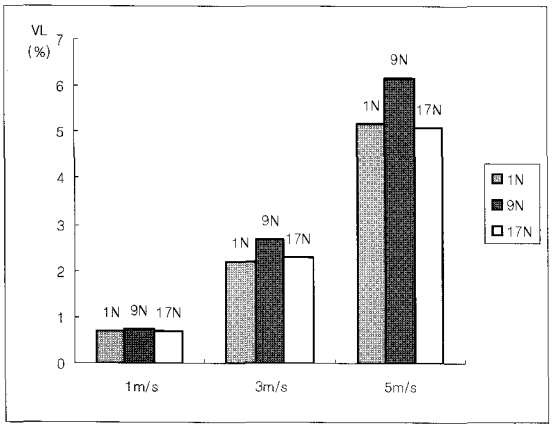
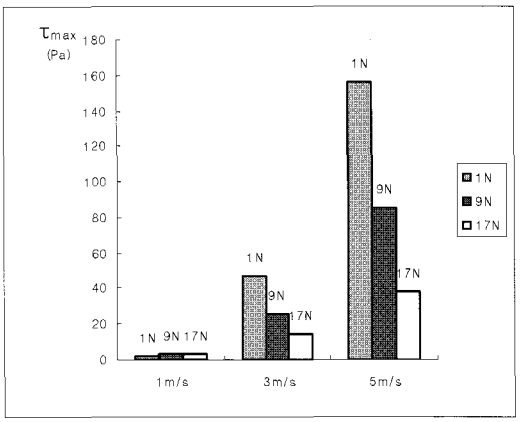


Figure 2. Percentage of volume lysed (VL%) of one (1N), nine (9N), and seventeen (17N) nozzle models for different ejecting velocities.

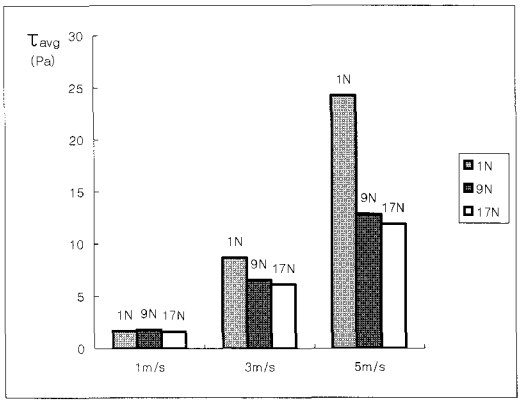
minutes were calculated from the lysis front velocities. Since the distance lysed into a clot was determined from the pressure, DL showed distributed value over the clot surface. The volume lysed (VL) was calculated by integrating DL over the surface area.

Since pressure-lysis velocity relationship was valid for the initial stage of clot lysis, we solved species transport equation with fluid flow equations. A clot was modeled as an isotropic porous medium, which is treated as a momentum sink in numerical calculation procedures. Once plasminogen activator (PA) 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.[12] 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



(a) Maximum wall shear stress



(b) Average wall shear stress

Figure 3. Maximum (τ_{max}) and average (τ_{avg}) wall shear stresses of one (1N), nine (9N), and seventeen (17N) nozzle models for different ejecting velocities.

assumed to be incompressible laminar Newtonian flow. Calculation domains were discretized, and the governing equations were solved. 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[13] by comparing our calculated results of clot lysis with the *in vitro* experimental data of Wu *et al* [11].

We assumed that 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.

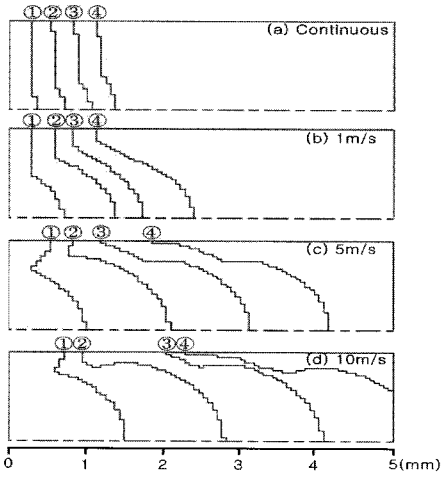


Figure 4. The lysis front positions in the symmetry plane of the vessel for continuous perfusion and intermittent injections. Symbol ①, ②, ③, ④ denotes the time at 5,10, 15, 20 minutes.

Finer grids were used near the nozzle exit. 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} cm^2 and high porosity (>0.9). 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 $5x10^{-7}cm^2/s$, which is is the typical protein diffusivity in the water phase of the gel. 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 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

Results

The velocity and pressure distributions were calculated

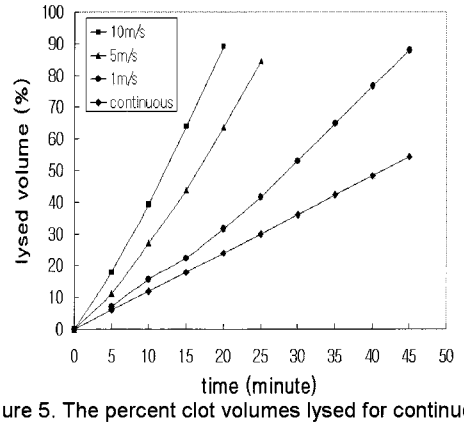


Figure 5. The percent clot volumes lysed for continuous infusion and intermittent injections with the period of five minutes for different injection.

for the ejecting velocity of 1, 3, and 5 m/sec. The pressure on the clot surface showed the maximum value at the stagnation point and decreased in the radial direction, following slight increase near the rim. High pressure zones were concentrated near the stagnation point and radial pressure gradients were higher in one nozzle model. Pressure was relatively uniformly distributed in the multi nozzle models. The maximum distances lysed into a clot in 5 minutes increased as the ejection velocity increased and decreased as the number of nozzles increased. It was up to 20 mm in the one nozzle model with 5 m/sec ejection velocity. Since the distance lysed into a clot was determined from the pressure, DL showed distributed value over the clot surface. The volume lysed (VL) was calculated by integrating DL over the clot surface area. We assumed a 2 cm long clot and the percentage of volume lysed (VL%) for different ejecting velocities were shown in Figure 2. The volume lysed increased as the velocity increases. We observed the negligible volume lysed for the small velocity (0.01 m/sec), but the volume lysed in 5 minute was about 7% of the clot volume for the ejecting velocity of 5 m/sec. The nine nozzles model showed about 20% increase of the lysed volume comparing to other models, but the one and seventeen nozzles models did not show significant differences. The maximum and average vessel wall shear stress were less than 160 Pa and 25 Pa for the velocity of 5 m/sec, and both values decreased as the number of nozzles increased (Figure 3). The average wall shear stress was smaller than 25 Pa, which implied that serious vessel damages were not expected.[14] In order to predict the effectiveness 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] 10μM urokinase solution was injected via a catheter. In continuous infusion, the flow rate was 1 ml/min. In order to study the effect of injection velocity, the 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 lysis front positions in continuous perfusion and intermittent injections are shown in Figure 4. Continuous perfusion dissolved the clot uniformly while forced injection dissolved the central region further, where the enzyme jet impinged. The percent volumes lysed (the ratio of dissolved clot volume to original clot volume) were calculated for the different injection velocities (Figure 5). In this model, intermittent injection accelerated clot lysis compared to continuous infusion, and its effectiveness was enhanced as the velocity increased.

Discussions

The difficulties in numerical modeling of thrombolysis were unsteadiness of dissolving process and the incomplete experimental data of pressure effects on lysis front velocity. We calculated the dissolved volume at the initial stage of thrombolysis process. As the clot dissolved, new blood - clot interface would be formed. Since the lysed distances and volumes should be calculated as the lysis front moved, unsteady calculation should be performed. Therefore, we developed a new thrombus lysis model based on quasi-steady species transport and reaction theory. 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 intra-luminal pressure by occlusion balloons has been attempted.[15] 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.[16] Forced intermittent injection would enhance enzyme permeation without increasing the infusion enzyme volume by decreasing the injection duration.

Our results showed that 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.

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 velocities 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, provide more resistance to perfusion,[17] therefore the effects of injection on enzyme perfusion may be different for various clots. Since thrombus is a very heterogeneous entity and its physical properties and compositions are diverse,[18] further study should be

performed in order to suggest appropriate injection parameters for the different clots. But our model study could provide some insight into the advantage of forced direct 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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