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A Numerical Study on the Effects of Drug Ejection Velocity on Endovascular Thrombolysis

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Abstract: Direct injection of a fibrinolytic agent to the intraarterial 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. In order to calculate the pressure distribution on the clot surface for different jet velocities (1, 3, 5 m/sec) and nozzle arrangements (1, 9, 17 nozzles), computational fluid dynamic methods were used. 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. The wall shear stress decreased as the number of nozzles increased, and the wall shear stress in most vessel wall was lower than 25 Pa. The results implied that thrombolysis could be accelerated by direct injection of a drug with the moderate velocity without damaging the blood vessel wall.

Key words: Thrombolysis, Infusion Velocity, CFD Modelling, Hemodynamics

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 high local 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. Mechanical methods, which are macerating clots using a mechanical device, have been used for chronic fibrous clots. 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 depend 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 are hard to be controlled by treatment schemes, but thrombolysis can be accelerated by enhancing the transport of pharmacological agents into a clot.

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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 distributed pressure applied by ejecting drug jets have not been studied. We would like to calculate pressure distribution on the clot surface 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 0.17 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 the 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 6.0) 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. The interface between blood and clot surface was modeled as a wall boundary. 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 [6,13].

If we simulate the clot lysis considering drug perfusion and lysis chemical reactions, many difficulties should be resolved. First, it is very difficult to define the physical properties of a blood clot. A clot is the porous media which are composed of fibrin fibers and blood cells. Physical properties of a clot depend on the cellular composition of a clot, fibrin fiber thickness and density, which vary depending on clot age and thrombotic process. Therefore it is very difficult to define representative values of porosities and permeation coefficients. Another difficulty is related to the chemical kinetics of lysis process. If we try to model clot lysis by considering permeation and reaction of a drug inside the clot, we need to know various parameters involved in reaction kinetics. Moreover unsteady nature of lysis process is difficult to model. Since the lysis process requires minimum reaction time for chemical reaction, quasi-steady modeling might be appropriate. But the time constants involved in several reaction cascade is hard to be determined.

Since many difficulties were involved in the porous media and chemical reaction model, we modeled the blood clot as a solid segment and used a simple relationship between the clot surface pressure and lysis velocity, which had been determined experimentally. 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.

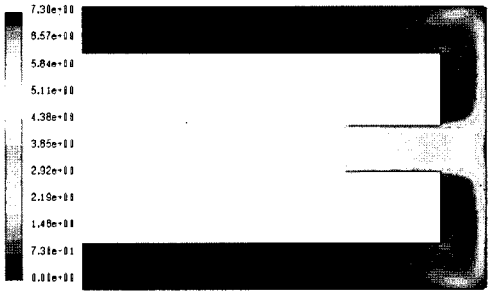
$$v = 0.0002\ P + 0.0129 \quad (r^2 = 0.98,\ r^2 : \text{correlation factor})$$

This relationship is valid on the in vitro whole blood clot. Since the physical properties of a clot depends on clot age and thrombotic process, different relationships could be used for other clots.

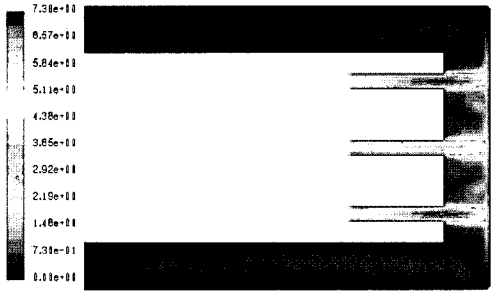
Considering the delay between the drug perfusion and the clot lysis, the distances lysed into clot (DL) in 5 minutes were calculated from the lysis front velocities. Since the distance lysed into a clot was determined from the pressure, DL showed distributed value over the clot surface. The volume lysed (VL) was calculated by integrating DL over the surface area.

RESULTS AND DISCUSSIONS

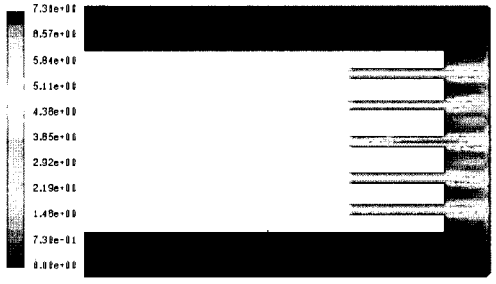
The velocity contours in the longitudinal cross section for the ejecting velocity of 5 m/sec were shown in Figure 1. In multiple jets, the interactions of jets caused the cross stream velocity diffusion. The fluid ejecting from the nozzle impinged on the clot surface, radially diffused and efflux to the proximal outlet boundary. The pressure on the clot surface showed the maximum value at the stagnation point and decreased radially, following slight increase near the rim (Figure 2). 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.



(a) one nozzle model

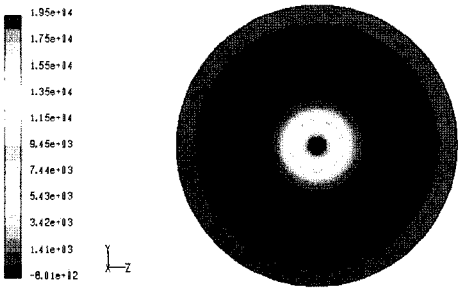


(b) nine nozzles model

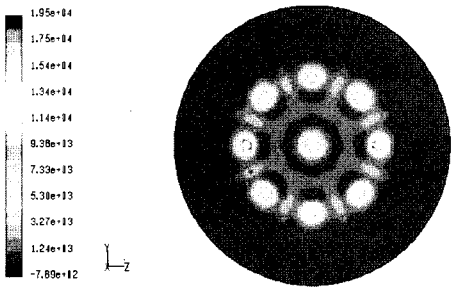


(c) seventeen nozzles model

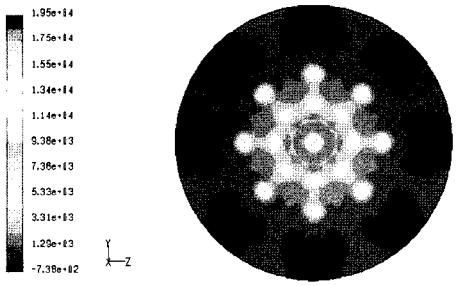
Fig. 1. Velocity contours at the longitudinal cross section for the velocity of 5 m/sec for one, nine, and seventeen nozzle models.



(a) one nozzle model



(b) nine nozzles model



(c) seventeen nozzles model

Fig. 2. Pressure distribution at the clot surface at the velocity of 5 m/sec for one, nine, and seventeen 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 3. 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.

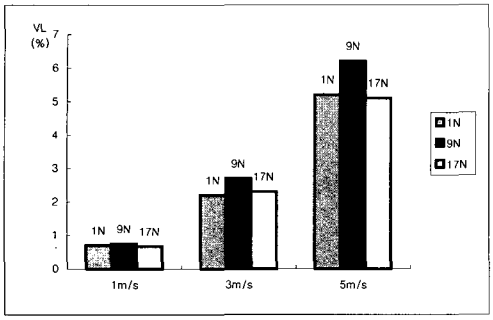
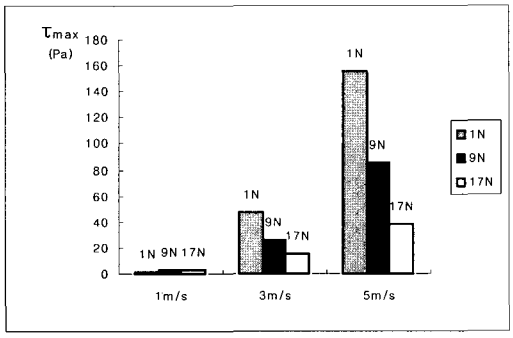


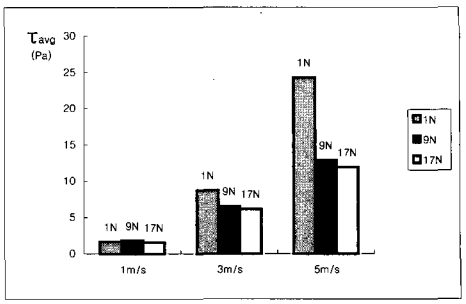
Fig. 3. Percentage of volume lysed (VL%) of one (1N), nine (9N), and seventeen (17N) nozzle models for different ejecting velocities.

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 4). The average wall shear stress was smaller than 25 Pa, which implied that serious vessel damages were not expected [14].

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. Also the experimental data on the pressure effects on the lysis process were available in the limited pressure ranges. Experimental studies of the pressure effects on the thrombolytic process should be performed.



(a) Maximum wall shear stress



(b) Average wall shear stress

Fig. 4. Maximum (τ_{max}) and average (τ_{avg}) wall shear stresses of one (1N), nine (9N), and seventeen (17N) nozzle models for different ejecting velocities

CONCLUSIONS

In order to study the effects of ejection velocity and nozzle arrangements on thrombolysis process, computational fluid dynamic methods were used. The pressure distribution on the clot surface and blood vessel wall shear stresses were calculated. Thrombolysis of a clot was 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 (up to 5 m/sec). The nine nozzles model showed about 20% increase of the lysed volume, and the one and seventeen nozzle models did not show significant differences. The wall shear stress decreased as the number of nozzle increased, and the wall shear stresses in most vessel wall were lower than 25 Pa. The results implied that thrombolysis could be enhanced by injecting a drug with the moderate velocity without damaging the blood vessel wall.

REFERENCES

[1] C. M. Smith, A. E. Yellin, F. A. Weaver, K. M. Li, and A. E. Siegel, *"Thrombolytic therapy for arterial occlusion; A mixed blessing"*, The American Surgeon, Vol. 60, pp.371-375, 1994.

[2] J. C. Chaloupka, S. Mangla, and D. C. Huddle, *"Use of mechanical thrombolysis via microballoon percutaneous transluminal angioplasty for the treatment of acute dural sinus thrombosis"*, Neurosurgery, Vol. 45, pp.650-657, 1999.

[3] T. M. Vesely, *"Mechanical thrombectomy devices to treat thrombosed hemodialysis grafts"*, Techniques in Vasc. & Interv. Radiol., Vol 6, pp.35-41, 2003.

[4] C. F. Dowd, A. M. Malek, C. C. Phatouros, and J. C. Hemphill, *"Application of a rheolytic thrombectomy device in the treatment of dural sinus thrombosis: a new technique"*, A.J.N.R., Vol. 20, pp. 568-570, 1999.

[5] M. Kobayashi, S. Sawada, N. Tanigawa, T. Senda, and Y. Okuda, *"Water jet angioplasty-an experimental study"*, Acta Radiologica, Vol.36, pp.453-456, 1995.

[6] R. K. Greenberg, K. Ouriel, S. Srivastava, C. Shortell, K. Ivancev, D. Waldman, K. Illig, and R. Green, *"Mechanical versus chemical thrombolysis: An in vitro differentiation of thrombolytic mechanism"*, J. Vasc. Interv. Radiol., Vol. 11, pp.199-205, 2000.

[7] S. L. Diamond, *"Engineering design of optimal strategies for blood clot dissolution"*, Ann. Rev, Biomed. Eng., Vol. 1, pp.427-461, 1999.

[8] J. P. Collet, C. Lesty, G. Montalescot, and J. W. Weisel, *"Dynamic changes of fibrin architecture during fibrin formation and intrinsic fibrinolysis of fibrin-rich clots"*, J. Biol. Chem., Vol. 278, pp. 21331-21335, 2003.

[9] M. Sabovic, and D. Keber, *"Factors influencing the lysis of ex vivo human thrombi"*, Fibrinolysis, Vol. 10, pp. 103-109, 1996.

[10] A. Blinc, D. Keber, G. Lahajnar, M. Stegnar, A. Zidansek, and F. Demsar, *"Lysis patterns of retracted blood clots with diffusion or bulk flow transport of urokinase into the clot: a magnetic resonance imaging study in vitro"*, Thromb. Haemostas., Vol. 68, pp.667-671, 1992.

[11] J. Wu, K. Siddiqui, and S. L. Diamond, *"Transport phenomena and clot dissolving therapy: An experimental investigation of diffusion controlled and permeation enhanced fibrinolysis"*, Thromb. and Hemostas., Vol.72, pp. 105-112, 1994.

[12] A. Blinc, S. D. Kennedy, R. G. Bryant, V. J. Marder, and C. W. Francis, *"Flow through clots determines the rate and pattern of fibrinolysis"*, Thromb. and Hemostas., Vol.71, pp. 230-235, 1994.

[13] G. Tratar, A. Blinc, M. Strukelj, U. Mikac, and I. Sersa, *"Turbulent axially directed flow od plasma promotes thrombolysis of non-occlusive whole blood clots in vitro"*, Vol 91, pp. 487-496, 2004

[14] D. L. Fry, "Acute vascular endothelrial changes associated with increased blood velocity gradients", Cir. Res., Vol. 22, pp. 165-182, 1968.