A Computational Model of Disseminated Intravascular Coagulopathy

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Objective: The PULSE initiative identified prevention of diffuse coagulopathies to be a priority in resuscitation science. Disseminated Intravascular Coagulopathy (DIC) is a significant complication of diseases such as sepsis and cancer. DIC involves the complex nonlinear interplay of the coagulation, fibrinolytic, and inflammatory systems (CIF). Its complexity poses a significant challenge for systematic clinical study; thus, modeling via computational approaches may prove to be a valuable adjunct. We developed a model of DIC using a 2-D Agent Based Model (ABM) implemented in the Netlogo modeling platform.

Methods: A 2-D particle system was developed in which particles move and interact on a discrete spatial grid composed of 'cells'. The particles of the system are cells (endothelial, WBC, platelets), cytokines, reactants, enzymes, and reaction products. The number of 'cells' used in the simulations is 5041 with approximately 500,000 agents. The agents' actions are determined by a set of rules derived from coagulation kinetics and cell behaviors. The system is designed to model a blood vessel *in vivo* including blood flow. The grid is in the shape of a rectangle. The sides of the rectangle represent endothelial cells and allow agents to interact with the endothelial cells or bounce off the walls. The ends are empty and allow the loss and introduction of agents. Blood flow is simulated by pulsatile movement of the particles through the system. The model is perturbed by the introduction of elevated levels of TNF-α in order to simulate the systemic inflammatory response from an insult such as sepsis.

Results: The simulation represents the formation of DIC due to elevated levels of TNF-α and subsequent activation of the inflammatory system. The activation of the coagulation system leads to the formation of microvasculature clot formation and a consumptive coagulopathy that results in the impairment of hemostasis. Table 1 demonstrates the alteration in the plasma levels of Antithrombin III (AT), Fibrinogen (F), platelet (plt), and Fibrin Split Products (FSP). As can be expected, the levels of AT, F and plts decrease as they are consumed by the systemic activation of the coagulation system, and the levels of FSP continue to increase as the clot is continually dissolved by the fibrinolytic system.

Conclusion: The simulation indicates that the effects of systemic inflammation on the CIF can be readily simulated using ABM. The ABM effectively modeled DIC as the end product of elevated cytokine levels as may be seen in sepsis. The demonstrated parameters and resultant coagulopathy are consistent with clinical DIC found in the literature. The goal in creating an ABM of DIC is to develop preclinical and clinical testing of therapies that may modulate the CIF to enhance patient outcomes.

Time (h)	AT (μM)	Fibrinogen (μM)	Platelet (x 10^9)	FSP(μg/mL)
0	4.50	88.20	300	0.0
1	4.37	83.74	291	0.3
4	3.65	74.91	271	2.7
8	2.74	64.29	227	6.0
12	1.80	29.63	39	33.5
16	1.07	22.06	11	37.5

Table 1: Plasma levels of AT, F, Plt, and FSP in DIC