A Short Contemporary History of Disseminated Intravascular Coagulation

Marcel Levi, MD, PhD[1] Tom van der Poll, MD, PhD[1,2,3]

[1] Department of Medicine, University of Amsterdam, Amsterdam, The Netherlands
[2] Center for Experimental and Molecular Medicine, University of Amsterdam, Amsterdam, The Netherlands
[3] Center for Infection and Immunity Amsterdam (CINIMA), Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Address for correspondence Marcel Levi, MD, PhD, Department of Medicine, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands (e-mail: m.m.levi@amc.uva.nl).

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Abstract

Disseminated intravascular coagulation (DIC) is a syndrome characterized by systemic intravascular activation of coagulation, leading to a widespread deposition of fibrin in the circulation. There is ample experimental and pathological evidence that the fibrin deposition contributes to multiple organ failure. The massive and ongoing activation of coagulation may result in depletion of platelets and coagulation factors, which may cause bleeding (consumption coagulopathy). The syndrome of DIC is well known in the medical literature for centuries, although a more precise description of the underlying mechanisms had to await the 20th century. Initial ideas on a role of the contact activation system as the primary trigger for the systemic activation of coagulation as well as a presumed hyperfibrinolytic response in DIC have been found to be misconceptions. Experimental and clinical evidence now indicate that the initiation of coagulation in DIC is caused by tissue factor expression, which in combination with downregulated physiological anticoagulant pathways and impaired fibrinolysis leads to widespread fibrin deposition. In addition, an extensive bidirectional interaction between coagulation and inflammation may further contribute to the pathogenesis of DIC.

Keywords

- disseminated intravascular coagulation
- history
- microvascular thrombosis
- tissue factor
- coagulation inhibitors
- fibrinolysis
- inflammation

History of DIC

Already in the 19th century, some of the first clinical and pathological observations related to disseminated intravascular coagulation (DIC) were made. One of the first reports comes from Dupuy in 1834, who describes the effect of the intravenous injection of brain material in animals.[1] The animals almost immediately died and at autopsy there were widespread clots in the circulation, presumably due to what we would now call tissue factor–dependent systemic activation of coagulation. After 30 years, Trousseau described the thrombotic tendency and the inclination of blood to clot in patients with advanced malignant disease.[2] In 1873, Naunyn showed that disseminated thrombosis could be evoked by intravenous injection of dissolved red cells, and Wooldridge demonstrated that the procoagulant involved was a substance contained in the stroma of the red cells.[3–5]

A more precise description of DIC and its underlying pathogenesis had to wait until 1955 when more insight into the mechanism of blood coagulation was attained and better laboratory tests had become available. Ratnoff et al carefully described the hemostatic abnormalities that occur in women with fetal death and amniotic fluid embolism.[6] The mechanism by which DIC can lead to bleeding was clarified only in 1961, when Lasch et al introduced the concept of consumption coagulopathy.[7] In 1965 McKay, who was to the first to realize that DIC was an "intermediary mechanism" in many diseases, published the first book on the DIC.[8]

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In subsequent years, the better understanding and the development of specific coagulation assays have enabled a more precise insight into the mechanisms that play a role in DIC.[9,10] Nevertheless, despite our increased knowledge and more refined therapy, the clinical management of patients with DIC often poses major difficulties for the modern clinician.

Manifestation of DIC

DIC is not a disease in itself, but it always occurs secondary to an underlying disorder (►**Table 1**). Nevertheless, signs and symptoms of DIC may be impressive and dominate the clinical picture. Patients with DIC may present with manifest thromboembolic disease or clinically less apparent microvascular thrombosis, which predominantly presents as multiple organ dysfunction.[9,11,12] Alternatively, severe bleeding may be the leading symptom. Quite often a patient with DIC has simultaneous thrombosis and bleeding, which does not facilitate a clinician's choice for the appropriate therapy. Interestingly, the clinical picture of a patient with DIC is oftentimes interpreted differently between specialists. Surgeons may primarily consider DIC as a bleeding disorder, whereas the (microvascular) thrombotic aspect is more often appreciated by hematologists and intensive care specialists. This different appraisal of DIC is also reflected in the many names that have been given to the disorder: defibrination syndrome,[13] consumption coagulopathy,[7] generalized intravascular coagulation,[14] thrombohemorrhagic phenomenon and consumptive thrombohemorrhagic disorder,[12] and more recently, disseminated intravascular fibrin formation.[15] In fact, both thrombosis and bleeding may occur at different locations and in varying intensity. The thrombotic spectrum ranges from laboratory signs of hypercoagulability without clinical significance to vast intravascular deposition of fibrin, which may jeopardize the circulation. Similarly, the intensity of bleeding spans from mild blood loss that is only present upon injury to spontaneous, massive and life-threatening bleeding.

Table 1 Clinical conditions that may be complicated by DIC

- Infectious diseases
  - Purpura fulminans
- Malignancy
  - Solid tumors
  - Leukemias
- Trauma
  - Brain injury
  - Burns
- Liver diseases
- Heat stroke
- Severe allergic/toxic reactions
  - Snake bites
- Vascular abnormalities/hemangiomas
  - Kasabach–Merritt syndrome
  - Other vascular malformations
  - Aortic aneurysms
- Severe immunologic reactions (e.g., transfusion reaction)
- Obstetrical conditions
  - Abruptio placentae
  - Amniotic fluid embolism
  - Preeclampsia/eclampsia
  - HELLP syndrome
  - Sepsis during pregnancy
  - Acute fatty liver

Abbreviation: DIC, disseminated intravascular coagulation.

Shift from Contact Activation to Tissue Factor–Mediated Coagulation Activation

It was initially thought that the systemic activation of coagulation in patients with sepsis was a result of direct activation of the contact system by microorganisms or endotoxin.[16] However, in the 1990s, it became apparent that the principal initiator of thrombin generation in sepsis is tissue factor and that the contact system is not involved. In patients with sepsis, activation of the contact system is detectable with assays for complexes between activated contact system factors and their inhibitors[17]; however, it was elegantly shown that blocking contact activation by means of a monoclonal antibody to factor XIIa did not affect *Escherichia coli*-induced coagulation abnormalities in baboons.[18] More recent experiments in a murine model of streptococcal necrotizing fasciitis showed no coagulopathy or bleeding, despite dramatically reduced factor XII and prekallikrein levels.[19] In endotoxemic humans, activation of factor XI did not result in contact system activation.[20] Hence, activation of the contact system may not be relevant for activation of coagulation. Instead, abrogation of the tissue factor/factor VII(a) pathway by monoclonal antibodies specifically directed against tissue factor or factor VIIa activity resulted in a complete inhibition of thrombin generation in endotoxin-challenged chimpanzees and prevented the occurrence of DIC and mortality in baboons that were infused with *E. coli*.[21–23] The contact system seems to play an important role in other physiologic and pathophysiologic mechanisms, most importantly on the occurrence of shock in sepsis and other underlying causes of DIC.[24,25] In clinical and experimental studies, contact system activation was associated with more severe hypotension.[24,26,27] Also, it was demonstrated that blocking contact system activation in experimental bacteremia in baboons prevented irreversible hypotension.[18] The mechanism by which the contact system affects the blood pressure regulation is most likely dependent on the formation and release of bradykinin and other kinins upon contact system activation. There is also emerging evidence that the contact system plays a role in fibrinolysis and complement activation in septic conditions.[28]

Emerging Role of Physiological Anticoagulant Pathways in DIC

In the past decades a very prominent role of physiological inhibitors of coagulation in the pathogenesis of DIC was identified. In general, procoagulant activity is regulated by three important anticoagulant pathways: the protein C system, antithrombin (AT) and tissue factor pathway inhibitor (TFPI); in DIC the function of all three pathways is impaired.[29]

There is ample evidence, starting from the first observations by the group of Esmon in the 1980s, that decreased function of the protein C pathway contributes to the derangement of coagulation in DIC.[30,31] In patients with DIC, the

protein C pathway malfunctions at virtually all levels. Plasma levels of the zymogen protein C are decreased because of impaired synthesis, consumption, and degradation by proteolytic enzymes, such as neutrophil elastase.[32–34] Furthermore, a significant downregulation of thrombomodulin, caused by proinflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-1, results in diminished protein C activation.[35,36] Low levels of free protein S may further compromise the function of the protein C system. In plasma, 60% of protein S is complexed with a complement regulatory protein, C4b binding protein (C4bBP), and exhibits no activity. The remaining protein S in plasma is free and functional. It was suggested that increased plasma levels of C4bBP caused by the acute phase reaction in inflammatory disease results in a relative protein S deficiency, which further contributes to a procoagulant state during sepsis. Indeed, infusion of C4bBP in combination with a sublethal dose of *E. coli* into baboons resulted in a lethal response with severe organ damage because of DIC.[37] In DIC, the endothelial protein C receptor (EPCR) is downregulated, which further impairs the function of the protein C pathway.[38] Sepsis can also cause resistance to activated protein C (APC) because of a substantial increase in factor VIII levels.[39]

The serine protease inhibitor AT is the main inhibitor of thrombin and factor Xa. In the 1970s, there was a major interest in the role of this coagulation inhibitor in DIC.[40,41] Without heparin, AT neutralizes coagulation enzymes in a slow, progressive manner.[42] Heparin induces conformational changes in AT that result in at least a 1,000-fold enhancement of AT activity. Thus, the clinical efficacy of heparin is attributed to its interaction with AT. Endogenous glycosaminoglycans, such as heparan sulfate, also promote on the vessel wall AT-mediated inhibition of thrombin and other coagulation enzymes. During severe inflammatory responses, AT levels are markedly decreased because of impaired synthesis, degradation by elastase from activated neutrophils, and consumption as a consequence of an ongoing thrombin generation.[43] Proinflammatory cytokines also cause reduced synthesis of glycosaminoglycans on the endothelial surface, thereby reducing AT function.[44]

A third inhibitory mechanism of thrombin generation involves TFPI, the main inhibitor of the tissue factor–factor VIIa complex and factor Xa. The role of TFPI in the regulation of DIC was intensely studied at the end of the previous century but has not been completely elucidated.[45,46] Administration of recombinant TFPI blocks inflammation-induced thrombin generation in humans, and pharmacological doses of TFPI prevent mortality during systemic infection and inflammation in experimental animals suggesting that TFPI can modulate tissue factor–mediated coagulation.[45,47]

From the Concept of Hyperfibrinolysis to Impaired Endogenous Fibrinolysis in DIC

Initially, it was thought that DIC was associated with a marked hyperfibrinolytic state. Indeed, in the course of DIC the fibrinolytic system may be activated concurrently with intravascular coagulation.[48,49] Animal experiments have demonstrated that the activation of fibrinolysis drastically intensifies the bleeding tendency.[50] Nevertheless, there are many indications that despite activation of the fibrinolytic system, plasmin generation is insufficiently capable of counteracting the intravascular fibrin formation.[51] The activation of fibrinolysis in the course of intravascular coagulation was considered a secondary phenomenon. More recent observations, however, point in the direction of a hypofibrinolytic state in the early phase of DIC. In fact, clinical and experimental studies indicate that the fibrinolytic system is essentially shut off during the initiation of DIC and may importantly contribute to the deposition of fibrin. In experimental models of DIC, fibrinolysis is initially activated, but subsequently inhibited, because of an increased release of plasminogen activator inhibitor-I (PAI-1) by endothelial cells.[22,52] These effects are mediated by TNF-α and IL-1.[53,54] In a study of 69 DIC patients, higher levels of tissue-type plasminogen activator antigen and PAI-1 with depressed levels of α2-antiplasmin were observed in patients with DIC and multiple organ failure compared with DIC patients without multiple organ failure.[55] This finding supports the conclusion that fibrinolysis is an important mechanism in preventing multiple organ failure. Experiments in mice with targeted disruptions of genes encoding components of the plasminogen–plasmin system confirm that fibrinolysis plays a major role in inflammation. Mice with a deficiency of plasminogen activators have a more extensive fibrin deposition in organs when challenged with endotoxin, whereas PAI-1 knockout mice, in contrast to wild-type controls, have no microvascular thrombosis upon endotoxin administration.[56] Thrombin-activatable fibrinolysis inhibitor (TAFI), like PAI-1, may play a role in impeding fibrinolysis and in augmenting formation of microvascular thrombi. Studies in a DIC cohort demonstrated very low levels of TAFI proportionate to thrombin generation in such patients, particularly in those with infection-associated DIC.[57] Hence, TAFI may contribute (along with PAI-1) to microvascular thrombosis-induced ischemia in organs resulting in multiple organ dysfunction.

An exception may be made for those rare cases of DIC, which are characterized by a severe hyperfibrinolytic state on top of an activated coagulation system. Examples of such situations are the DIC that occurs as a complication of acute promyelocytic leukemia (acute myeloid leukemia M-3, according to the French–American–British classification) or the DIC that may occur secondary to some forms of prostatic cancer.[58,59] Although hyperfibrinolysis predominates in this situation, disseminated thrombosis is found in a considerable number of patients at autopsy.[60] Clinically, these patients suffer from severe bleeding, which (in contrast to most other forms of DIC) may benefit from therapy with antifibrinolytic agents.[61]

Bidirectional Interaction between Coagulation and Inflammation

For many decades now it has been established that the procoagulant changes in DIC are caused by inflammatory mediators and cells. Indeed, many of these interactions have been identified in experimental and clinical studies.[62] Recent studies, however, have demonstrated that coagulation

proteases and protease inhibitors not only interact with coagulation protein zymogens, but also with specific cell receptors to induce signaling pathways. In particular, protease interactions that affect inflammatory processes may be important in DIC. The pivotal mechanism by which coagulation proteases modulate inflammation is by binding to protease activated receptors or PARs. Four types (PAR 1–4) have been identified; all belonging to the family of transmembrane domain, G-protein-coupled receptors.[63] A typical feature of PARs is that they serve as their own ligand. Proteolytic cleavage by an activated coagulation factor leads to exposure of a neoamino terminus, which activates the same receptor (and possibly adjacent receptors), initiating transmembrane signaling. PARs are localized in the vasculature on endothelial cells, mononuclear cells, platelets, fibroblasts, and smooth muscle cells.[63] PARs 1, 3, and 4 are thrombin receptors and PAR-1 can also serve as a receptor for the tissue factor–factor VIIa complex and factor Xa. PAR-2 cannot bind thrombin, but can be activated by the tissue factor–factor VIIa complex or factor Xa. Binding of thrombin to its cellular receptor may induce the production of several cytokines and growth factors. Binding of tissue factor–factor VIIa to PAR-2 also results in upregulation of inflammatory responses (production of reactive oxygen species and expression of MHC class II and cell adhesion molecules) in macrophages and was shown to affect neutrophil infiltration and proinflammatory cytokine (TNF-α, IL-1β) expression. The in vivo relevance of PARs has been confirmed in various experimental studies using PAR inhibitors or PAR-deficient mice.[64,65]

There is compelling evidence that besides their role as an important regulator of coagulation activity, physiological anticoagulants also have an important function in modulating inflammation.[66,67] APC plays an important role in attenuating the systemic inflammatory response in sepsis as demonstrated in experiments showing that blocking the protein C pathway in septic baboons exacerbated the inflammatory response. In contrast, administration of APC ameliorated the inflammatory activation upon the intravenous infusion of *E. coli*.[68] Similar experiments in rodents showed identical results and demonstrated a beneficial effect on inflammatory effects in various tissues.[69] Support for the notion that APC has anti-inflammatory properties come from in vitro observations, demonstrating an APC binding site on monocytes, that may mediate downstream inflammatory processes,[70,71] and from experiments showing that APC can block nuclear factor κB nuclear translocation, which is a prerequisite for increases in proinflammatory cytokines and adhesion molecules.[72] These in vitro findings are supported by in vivo studies in mice with targeted disruption of the protein C gene. In these mice with genetic deficiencies of protein C, endotoxemia was associated with a more marked increase in proinflammatory cytokines and other inflammatory responses as compared with wild-type mice.[73,74] Apart from its effect on cytokine levels, APC has been shown to inhibit leucocyte chemotaxis and adhesion of leukocytes to activated endothelium.[75,76] This notion was confirmed in a hamster endotoxemia model at concentrations of recombinant human APC (rhAPC) that preclude a significant anticoagulant effect.[77] Moreover, in a human model of endotoxin-induced pulmonary inflammation, systemic administration of rhAPC resulted in significant local anti-inflammatory effects.[78] A potential mechanism is that APC inhibits expression of platelet-derived growth factor in the lung.[79] In addition, it has been shown that APC protects against the disruption of the endothelial cell barrier in sepsis, probably by interfering with EPCR and PAR-1 on endothelial cells.[80] Finally, APC is capable of inhibiting endothelial cell apoptosis, which also seems to be mediated by an EPCR-PAR-1-dependent mechanism.[81,82]

In recent years increasing evidence has been accumulated suggesting that AT also possesses potent anti-inflammatory properties independent of its anticoagulation activity.[83] Perhaps most importantly, AT induces prostacyclin release from endothelial cells.[84,85] Prostacyclin inhibits platelet activation and aggregation, blocks neutrophil tethering to blood vessels, and decreases endothelial cell production of various cytokines and chemokines.[86] Additional anti-inflammatory actions of AT are mediated by direct interaction with leukocytes and lymphocytes. Antithrombin binds to receptors, such as syndecan-4, on the cell surfaces of neutrophils, monocytes, and lymphocytes and blocks the interaction of these cells with endothelial cells.[87] Inhibition of leukocyte–endothelial cell interactions by AT may be mediated by prostacyclin release, downregulation of P-selectin, or prevention of leukocyte activation.[85] Thus, AT directly hinders leukocyte migration and adhesion to endothelial cells, which in turn impacts the severity of capillary leakage and subsequent organ damage.

Diagnosis and Treatment of DIC in the Past Two Decades

Over the past 20 years the diagnosis of DIC has been greatly facilitated by the development of scoring algorithms. For the diagnosis of overt DIC a simple scoring system has been developed by the subcommittee on DIC of the International Society on Thrombosis and Hemostasis (ISTH).[88] The score can be calculated based on routinely available laboratory tests, that is, platelet count, prothrombin time, a fibrin-related marker (usually D-dimer), and fibrinogen. Tentatively, a score of five or more is compatible with DIC, whereas a score of less than five may be indicative but is not affirmative for nonovert DIC. For nonovert DIC more refined scoring systems have been developed, which are currently being evaluated.[89] By using receiver operating characteristic curves, an optimal cutoff for a quantitative D-dimer assay was determined, thereby optimizing sensitivity and the negative predictive value of the system.[90] Prospective studies show that the sensitivity of the DIC score is 93%, and the specificity is 98%.[91,92] Studies in a series of patients with specific underlying disorders causing DIC (e.g., cancer patients or patients with obstetric complications) shows similar results.[93,94] The severity of DIC according to this scoring system is related to the mortality in patients with sepsis.[95] Linking prognostic determinants from critical care measurement scores such as

Acute Physiology and Chronic Health Evaluation (APACHE-II) to DIC scores is an important means to assess prognosis in critically ill patients. Similar scoring systems have been developed and extensively evaluated in Japan.[96] The major difference between the international and Japanese scoring systems seems a slightly higher sensitivity of the Japanese algorithm, although this may be due to different patient populations (Japanese series typically includes relatively large numbers of patients with hematological malignancies).

The rule that adequate management of patients with DIC depends on a vigorous treatment of the underlying disorder to alleviate or remove the inciting injurious cause has not been challenged for decades and remains the cornerstone of treatment. However, supportive treatment aimed at the coagulopathy has been developed and may form an addition to intensive support of vital functions.[97] These supportive treatment options consist of anticoagulant treatment, administration of coagulation inhibitor concentrates, and specific interventions aimed at the fibrinolytic system in selected patients.[98] The concept that a single intervention, such as administration of AT concentrate or infusion of rhAPC is effective to reduce mortality in patients with DIC has never been confirmed in randomized controlled trials; however, these interventions may be helpful as adjunctive treatment strategies.

Conclusion

DIC is a complication of a myriad of underlying disorders and has been recognized as an important and complex clinical entity for centuries. The pathogenesis of DIC has for the major part been elucidated in the past few decades and this knowledge has been helpful in better defining diagnostic criteria for DIC and in developing supportive therapeutic interventions.

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