Disseminated intravascular coagulation in cardiac arrest and resuscitation

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Abstract
The aims of this review are to demonstrate that the changes in coagulation and fibrinolysis observed in cardiac arrest and resuscitation can be recognized as disseminated intravascular coagulation (DIC), and to discuss the probability of DIC being a therapeutic target. The appearance of triggers of DIC, such as damage-associated molecular patterns, inflammatory cytokines, and adrenaline, is associated with platelet activation, marked thrombin generation and fibrin formation, insufficient anticoagulation pathways, and increased fibrinolysis by tissue-type plasminogen activator, followed by the suppression of fibrinolysis by plasminogen activator inhibitor-1, in patients with cardiac arrest and resuscitation. Simultaneous neutrophil activation and endothelial injury associated with glycocalyx perturbation have been observed in these patients. The degree of these changes is more severe in patients with prolonged precardiac arrest hypoxia and long no-flow and low-flow times, patients without return of spontaneous circulation, and non-survivors. Animal and clinical studies have confirmed decreased cerebral blood flow and microvascular fibrin thrombosis in vital organs, including the brain. The clinical diagnosis of DIC in patients with cardiac arrest and resuscitation is associated with multiple organ dysfunction, as assessed with the sequential organ failure assessment score, and increased mortality. This review confirms that the coagulofibrinolytic changes in cardiac arrest and resuscitation meet the definition of DIC proposed by the ISTH, and that DIC is associated with organ dysfunction and poor patient outcomes. This evidence implies that established DIC should be considered to be one of the main therapeutic targets in post-cardiac arrest syndrome.

KEYWORDS
cardiac arrest, disseminated intravascular coagulation, fibrinolysis, inflammation, resuscitation

1 | INTRODUCTION

Sepsis, trauma and cardiac arrest are three major insults to the body that elicit systemic inflammation known as systemic inflammatory response syndrome (SIRS).1,2 Close interplay between innate immune inflammation and coagulation has been well recognized.2 which suggests that coagulation occupies an important place in the innate immune inflammatory system.4 Disseminated intravascular coagulation (DIC), which is recognized as dysregulated coagulofibrinolytic responses against such insults, is a frequent complication of SIRS.5 In fact, recent review articles have shown the importance of bidirectional interactions between inflammation and coagulation in the pathophysiology of DIC.6 Sepsis and trauma have long been recognized as major conditions that can evoke DIC; however, cardiac arrest and resuscitation, which amount to whole-body ischemia and
reperfusion, have not been acknowledged as basic conditions associated with DIC.7

The Scientific Standardization Subcommittee (SSC) on DIC of the ISTH proposed the following key pathophysiologic conditions for DIC: generalized inflammatory responses with the release of inflammatory cytokines, and intravascular activation of coagulation with loss of localization that can originate from and cause damage to the microvascular endothelium, which is associated with the subsequent consumption and exhaustion of platelets and coagulation factors.7 In addition, the impairment of natural anticoagulant pathways and the inhibition of fibrinolysis contribute to the development of DIC.6-8 If these changes are sufficiently severe, DIC can produce organ dysfunction through microvascular thrombosis, and it therefore affects the patient’s outcome.6-8

This review focuses on evidence that cardiac arrest and resuscitation are conditions that lead to the development of DIC. After the acknowledgment that the coagulofibrinolytic changes represent DIC, the importance of the diagnosis of DIC as a therapeutic target in post–cardiac arrest syndrome will be discussed.

2 | HISTORICAL PERSPECTIVE

Approximately half a century ago, an experimental study on cardiac arrest and resuscitation demonstrating intravascular clot formation was performed.9 Mackey subsequently reported, for the first time, that anoxemia and cardiac arrest, which are the most typical examples of shock, are systemic factors that lead to DIC.10 Mehta et al11 provided laboratory evidence of DIC after cardiac arrest, and noted that these changes occurred independently of the underlying diseases causing the cardiac arrest. Rabbit brains subjected to total cerebral ischemia were found to have microvascular obstruction, which was called the no-reflow phenomenon.12 Diverse etiologies, including intravascular clotting, have been considered to constitute the pathogenesis of this postischemic cerebral injury. Safer13 discussed how, in addition to cerebral no-reflow, global hypoperfusion after cardiac arrest and resuscitation, which probably results from microcirculatory obstruction due to multiple factors, including intravascular coagulation, give rise to organ dysfunctions, and named this phenomenon postresuscitation syndrome. From the end of the 1990s to the early 2000s, by the use of sensitive molecular markers of coagulation, massive thrombin generation and fibrin formation with subsequent impairment of fibrinolysis associated with insufficient activity of the protein C-thrombomodulin pathway were observed in patients after cardiac arrest and resuscitation.14,15 The International Liaison Committee on Resuscitation (ILCOR) Consensus Statement renamed postresuscitation syndrome post–cardiac arrest syndrome, and proposed that the systemic ischemia and reperfusion responses associated with SIRS and increased coagulation are important factors in the clinical manifestation of multiple organ dysfunction.2 A recent review article implied that the coagulofibrinolytic changes in patients with post–cardiac arrest syndrome could be considered to be DIC.16

3 | INFLAMMATION AND COAGULATION

3.1 | Damage-associated molecular patterns

In both sepsis and trauma, damage-associated molecular patterns (DAMPs), such as histones and mitochondrial DNA released in response to cellular injury, constitute a key link between inflammation and coagulation through the expression of inflammatory cytokines and microvascular thrombosis, which leads to organ injury.17,18 Recent evidence suggests that hypoxia, ischemia and reperfusion also result in the release of histones because of tissue injury, giving rise to organ dysfunction.19 Upon stimulation with infectious and non-infectious insults, neutrophils release neutrophil extracellular traps (NETs) presenting matrix DNA and histones with neutrophil components, such as neutrophil elastase and matrix metalloprotease 9.20 In the circulation, free or DNA-complexed (nucleosome) histones and cell-free DNA have been shown to be released by NETosis, and after tissue injury.6,19,21 Extracellular histones, cell-free DNA and NETs formation are now recognized as major contributors to the development of DIC (Figure 1). Clinical studies have shown correlations between DNA-histone complexes, cell-free DNA, NETosis and DIC, and therefore support this notion.22,23

High levels of DAMPs, such as DNA-histone complexes and cell-free DNA, observed in patients after cardiac arrest and resuscitation, especially non-survivors, showed that whole-body hypoxia, ischemia and reperfusion result in release of the main triggers of DIC.24,25

3.2 | Pattern recognition receptors

Ischemia and reperfusion cause inflammation via the signal transduction of DAMPs through pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs).26 TLR2 and TLR4 are located on the surfaces of cell membranes, and interleukin (IL)-1 receptor-associated kinase 4 (IRAK4) is involved in their signal transduction pathways. NLR family pyrin domain-containing 3 (NLRP3), a subtype of NLR that is located in the cytoplasm, is recognized to form inflammasomes, and leads to the production of pro-IL-1β and its conversion to IL-1β.
Monocytes purified from the blood of patients after cardiac arrest and resuscitation showed upregulation of TLR2, TLR4, IRAK4, and NLRP3 mRNAs from the early period (~12 hours) to the late period (~48 hours) after emergency department (ED) admission. In the early period, the serum lactate level, which is a surrogate marker of ischemia, is positively correlated with monocyte expression of TLR2, TLR4, and IRAK4. In parallel with these changes, significant upregulation of IL-1β mRNA levels was observed. Therefore, DAMPs combine with PRRs and then activate their signal transduction, leading to the expression of inflammatory cytokines after cardiac arrest and resuscitation.

### 3.3 Inflammatory cytokines

DAMPs induce the expression of inflammatory cytokines and chemokines through PRRs and their signaling, which, if the insults that release DAMPs are sufficiently severe, give rise to SIRS associated with DIC. Actually, histones were shown to increase tumor necrosis factor (TNF-α) and IL-6 levels within 2 hours after infusion in mice. Abrams et al. suggested that the IL-6 stored in neutrophils, lymphocytes and monocytes is probably released immediately after histone infusion. TNF-α infusion in normal subjects increased the generation of thrombin and plasmin. This was followed by the inhibition of fibrinolysis by plasminogen activator inhibitor-1 (PAI-1). Thus, it was hypothesized that TNF-α is the primary cytokine that gives rise to DIC. However, Levi et al. later demonstrated that IL-6 rather than TNF-α is the responsible cytokine in the pathogenesis of thrombin generation, and that TNF-α contributes to fibrinolytic responses in DIC.

High levels of TNF-α and IL-6 have been repeatedly confirmed in patients after cardiac arrest and resuscitation from immediately after arrival at the ED to several days later. The levels of both cytokines were higher in patients with a longer low-flow time (time of cardiopulmonary resuscitation [CPR]), patients with catecholamine use, and non-survivors, and contributed to the development of SIRS. The IL-6 level was correlated with both the lactate level and sequential organ failure assessment (SOFA) score, and was an independent predictor of in-hospital death of the patients.

### 3.4 The neuroinflammatory circuit

The activation of the insult-induced hypothalamic-pituitary-adrenal axis has been well recognized. In addition to this response, insults also activate the sympathetic paraganglionic neurons in the spinal cord through both the rostral ventrolateral medulla and the locus coeruleus, and this is followed by the release of adrenaline and noradrenaline from the adrenal medulla and celiac ganglion. The systemic increases in the levels of inflammatory cytokines, especially IL-1, activate these neuroinflammatory circuits, leading to the release of catecholamines. Although some controversies exist, IL-1 is considered to be a potent stimulator of both coagulation and fibrinolysis, and IL-1 has been shown to inhibit fibrinolysis via expression of PAI-1. The catecholamine-induced activation of coagulation that leads to microvascular fibrin thrombosis and DIC has also long been acknowledged.

High levels of IL-1 and catecholamine were observed in patients after cardiac arrest and resuscitation. Furthermore, IL-1 mRNA expression and its protein production by monocytes was confirmed in these patients. Extremely high levels of adrenaline, approximately 2700 times greater than the normal range, may occur because of exogenous administration of adrenaline during CPR. One study suggested a close association between the sympathoadrenal activation-induced increase in catecholamine levels and endothelial injury, as assessed by the measurement of soluble
thrombomodulin. These results showed the existence of an association between both adrenalinues produced by neuroinflammatory activation and those administered exogenously with the development of DIC after cardiac arrest and resuscitation.

4 | PLATELET ACTIVATION AND EXHAUSTION

In cardiac arrest and resuscitation, platelet activation with reduced platelet counts has been confirmed by use of the measurement of thromboxane (TX) B2 and 11-dehydro-TXB2 (metabolites of TXA2), platelet factor 4, mean platelet volume, and ADP closure time. The levels of these markers of activation and decreases in platelet counts were more pronounced in patients with a poor outcome. Whereas platelets are activated, both the aggregation induced by ADP, adrenaline and collagen and the aggregation assessed by impedance aggregometry were below the normal range. Platelet counts were more pronounced in patients with a poor outcome. Whereas platelets are activated, both the aggregation induced by ADP, adrenaline and collagen and the aggregation assessed by impedance aggregometry were below the normal range.41,45 A swine model of cardiac arrest also showed decreased platelet counts and reduced platelet contraction and aggregation during and after CPR. These reduced platelet function with low platelet counts may explain the massive activation-induced platelet exhaustion that occurs because of depletion of the platelet storage pool, which is often observed in patients with DIC. Hypoxia, ischemia, thrombin and catecholamines are well-known activators of platelets. Increases in all of these have been observed in patients after cardiac arrest and resuscitation. Recently, histones have been reported as other activators of platelets, and a histone-induced decline in platelet counts was observed in critically ill patients. Platelet activation results in a thromboinflammatory state due to the expression and generation of tissue factor, thrombin, and IL-1, which may further enhance the development of DIC.6,8,50

5 | TISSUE FACTOR AND MASSIVE THROMBIN GENERATION

Along with platelet activation, tissue factor-mediated coagulation activation followed by thrombin generation is a principal initiator of DIC. In addition to the DAMP-induced and inflammatory cytokine-induced expression of tissue factor on mononuclear cells and endothelial cells, endothelial cells that are perturbed by hypoxia and ischemia contribute to the expression of tissue factor. Hypoxia-induced direct endothelial injury may expose the tissue factor present in perivascular cells to the systemic circulation. Tissue factor levels significantly increased immediately after arrival at the ED, and remained high from CPR to 24 hours after the return of spontaneous circulation (ROSC). In accordance with the changes in tissue factor levels, massive thrombin generation, as assessed by the measurement of fibrinopeptide A, with marked fibrin formation was observed in patients after cardiac arrest and resuscitation. Increased thrombin levels, as assessed by the measurement of thrombin-antithrombin complex (TAT), fibrin monomers, and soluble fibrin, were also confirmed in patients after cardiac arrest and resuscitation, from the prehospital setting until 3 days after successful CPR. Importantly, thrombin generation was greater in patients who died without achieving ROSC or in the hospital and patients with a long no-flow time (in cardiac arrest without CPR) or low-flow time than in survivors and patients with a short low-flow time.

6 | NEUTROPHIL ACTIVATION AND ENDOTHELIAL INJURY

Neutrophil and endothelial cell interactions through cell adhesion molecules such as selectins, integrins and the immunoglobulin superfamily are important processes during inflammation. TNF-α, IL-1 and thrombin are potent activators of neutrophils and endothelial cells, and the levels of all of these are increased during cardiac arrest and resuscitation. Hypoxia elicits neutrophil and endothelial activation; if sufficiently severe, hypoxia and neutrophils can injure endothelial cells. Activated neutrophils therefore play central roles in reperfusion-induced tissue injury via the production of reactive oxygen species and the release of components such as elastase. These processes promote the activation of coagulation and impairment of anticoagulation systems, and then lead to organ dysfunction.

6.1 | Neutrophil activation

Neutrophil activation, as measured according to neutrophil elastase (neutrophil elastase and α1-protease inhibitor complex) and soluble L-selectin levels, was confirmed from the time of CPR to 24 hours after successful ROSC. The levels of neutrophil elastase were higher in patients without ROSC than in those in whom resuscitation was achieved, and were correlated with the duration of cardiac arrest, which suggests that prolonged hypoxia and ischemia induce greater activation of neutrophils. Neutrophil elastase has been implicated in neutrophil-mediated tissue and endothelial injury. Elevated neutrophil elastase levels were associated with parallel increases in the levels of soluble thrombomodulin. Soluble thrombomodulin is formed by the limited proteolysis of endothelial thrombomodulin by neutrophil elastase, which is recognized as a marker of endothelial injury. Thus, the neutrophil activation-induced release of elastase may be considered to be one of the causes of endothelial injury during cardiac arrest and resuscitation.

6.2 | Endothelial activation and injury

High soluble thrombomodulin levels in patients after cardiac arrest and resuscitation were also confirmed in three other studies, which firmly established the existence of endothelial injury. Furthermore, endothelial activation has also been recognized in these patients. Endothelial activation can be measured as increases in the levels of soluble forms of cell adhesion molecules. Increases in the
levels of soluble forms of P-selectin, E-selectin, ICAM-1 and VCAM-1 have been repeatedly confirmed during and after cardiac arrest and resuscitation.\textsuperscript{62-64} Endothelial activation and injury were associated with a high prevalence of SIRS and poor outcomes, as assessed according to high in-hospital mortality, low survival probability, and unfavorable Cerebral Performance Category (CPC) levels.\textsuperscript{39,68,69}

Glycocalyx overlying the endothelial cell surface functions as a barrier between the circulating blood and endothelium through the maintenance of normal vascular physiology, including coagulation and vascular permeability.\textsuperscript{70} It is important to keep in mind that capillary leakage is one of the main characteristics of DIC.\textsuperscript{7} The main constituents of glycocalyx are the above-mentioned cell adhesion molecules (glycoproteins), and proteoglycans such as syndecan and glypicans. Both are bound to the endothelial cells, with proteoglycans connecting to glycosaminoglycans. Inflammatory cytokines such as TNF-\(\alpha\) and neutrophil activation-derived elastase, matrix metalloproteases and reactive oxygen species induce glycocalyx shedding. If the insults are sufficiently severe, glycocalyx perturbation develops, and this is followed by increased vascular permeability and derangement of the coagulation systems.\textsuperscript{70}

Sepsis and the trauma associated with SIRS are two major pathologic conditions that elicit glycocalyx perturbation.\textsuperscript{70} Focal ischemia and reperfusion injury are also involved in these pathologic conditions.\textsuperscript{70} These studies, as well as the neutrophil activation and endothelial injury observed following cardiac arrest and resuscitation, suggest the destruction of glycocalyx in these patients. Indeed, high levels of syndecan-1, one of the major proteoglycans, were observed to be correlated with the CPR time in patients after cardiac arrest and resuscitation.\textsuperscript{68,71} Furthermore, elevated plasma levels of glycosaminoglycans, heparan sulfate and hyaluronic acid were also observed in these patients.\textsuperscript{71}

Thus, cardiac arrest and resuscitation are associated with neutrophil activation and endothelial injury with glycocalyx destruction, which are the main pathophysiologies of DIC.\textsuperscript{6-8}

7 | IMPAIRMENT OF ANTICOAGULATION PATHWAYS

Tissue factor pathway inhibitor (TFPI) blocks tissue factor-activated factor VIIa complex and activated FX (FXa), activated protein C inhibits activated FV and activated FVIII by proteolytic degradation, and antithrombin inhibits FXa, activated FIX, and activated FII (thrombin), which are three major natural anticoagulation pathways.\textsuperscript{8} During DIC, all three pathways can be impaired by reduced synthesis, increased consumption, extravasation due to increased capillary leakage, and cleavage by neutrophil elastase.\textsuperscript{8,72-74} TFPI and antithrombin bind to glycocalyx via heparan sulfate.\textsuperscript{70} Conversion of protein C to activated protein C occurs via thrombomodulin, which binds to endothelial cells. Thus, glycocalyx degradation and endothelial injury give rise to malfunction of three anticoagulant pathways.

As mentioned above, many studies have confirmed neutrophil activation, glycocalyx degradation and endothelial injury in patients after cardiac arrest and resuscitation. An in vitro experimental study showed that hypoxia increases endothelial perturbation and decreases thrombomodulin functional activity in association with the suppression of mRNA expression, leading to the production of FX activator, which promotes coagulation.\textsuperscript{75} The levels of protein C (antigen and activity) and protein S activity in non-survivors and patients without ROSC were reported to be lower than those in survivors and healthy volunteers after successful CPR.\textsuperscript{15,76} Low protein C levels and the impaired production of activated protein C, along with highly soluble thrombomodulin, suggest malfunction of the protein C anticoagulant pathway because of endothelial injury.\textsuperscript{15} The TFPI levels of patients with cardiac arrest immediately after arrival at the ED were significantly lower than the levels of normal subjects.\textsuperscript{55} In addition, the TFPI levels did not match the increased levels of tissue factor from arrival at the ED to 24 hours after admission in patients with ROSC after cardiac arrest. Low levels of antithrombin were also confirmed in patients after cardiac arrest and resuscitation, especially in non-survivors and patients with DIC.\textsuperscript{15,77,78} An experimental study supported these results, showing that antithrombin levels decrease with mirror-image increases in TAT levels after CPR in a pig cardiac arrest model.\textsuperscript{79}

8 | DETERIORATION OF FIBRINOLYTIC SYSTEMS

Persistent suppression of fibrinolysis by PAI-1 is one of the main characteristics of DIC.\textsuperscript{5,8,80} DAMPs, especially high levels of cell-free DNA, and inflammatory cytokines such as TNF-\(\alpha\) and IL-1, have been suggested as causes of inactivation of tissue-type plasminogen activator (t-PA) by PAI-1 and the induction of PAI-1 activity.\textsuperscript{6,31,37} Importantly, TNF-\(\alpha\) and IL-1 initially increased both thrombin generation and fibrinolytic activity as measured according to t-PA activity, and this was followed by the appearance of PAI-1 activity at 3-4 hours after their administration.\textsuperscript{31,37} Hypoxia, hypoxia-induced cytokines and thrombin immediately trigger the release of stored t-PA from Weibel-Palade bodies into the systemic circulation,\textsuperscript{82} whereas the expression of t-PA mRNA during hypoxia either remain unchanged or decrease, according to the findings of in vitro and in vivo studies.\textsuperscript{83,84} Mice with decreased t-PA mRNA levels showed increased PAI-1 activity in the plasma (4 hours) and PAI-1 mRNA levels (6 hours) in the lung after exposure to hypoxia, which led to pulmonary vascular thrombosis.\textsuperscript{85} These experimental studies indicate a time difference in the appearance of t-PA and PAI-1 activities, which suggests that increased fibrinolysis is followed by the suppression of fibrinolysis after cardiac arrest and resuscitation.

8.1 | Early phase

Massive plasmin generation and fibrin formation, as measured according to fibrinopeptide B\textsubscript{315-42} and D-dimer levels, respectively,
were associated with marked increases in t-PA activity and antigen levels from immediately after arrival at the ED to the time of ROSC or cessation of CPR in patients with out-of-hospital cardiac arrest (Figure 2). During this phase, no PAI-1 activity was observed and antigen levels, which measure t-PA/PAI-1 complex and active PAI-1, showed only mild elevations. These changes were followed by a decline and then the complete disappearance of t-PA activity and a significant increase in PAI-1 activity from 1 to 24 hours after presentation to the ED. The results suggest that increased fibrinolysis due to the release of t-PA in the early phase of cardiac arrest and resuscitation immediately switched to suppression of fibrinolysis by PAI-1 in the later phase. Importantly, extreme thrombin generation always underlies these fibrinolytic changes, and this remains high for 24 hours.14

**FIGURE 2** Massive thrombin generation and fibrin formation are associated with changes in fibrinolysis. Fibrinolytic activity assessed by tissue-type plasminogen activator (t-PA) initially increased, then completely disappeared by plasminogen activator inhibitor-1 (PAI-1) (time point 4, †††). The duration of increased fibrinolysis is very short, and there is an immediate switch to suppression of fibrinolysis. Importantly, thrombin generation is persistently increased by approximately 200 times on arrival at the emergency department (ED) (time point 1), and remains approximately 10 times higher even at 24 hours after arrival (time point 4) in comparison with normal reference values. Death: the patients died without spontaneous return of circulation (ROSC). Resuscitation: the patients with ROSC. FPA, fibrinopeptide A, a marker of thrombin generation and its direct action on prothrombin; FPB_{β15-42}, fibrinopeptide B\_β15-42, a marker of plasmin generation and its direct action on fibrin. Time point 1: immediately after arrival at the ED. Time point 2: cessation of cardiopulmonary resuscitation (patients without ROSC) or 30 minutes after arrival at the ED. Time point 3: 60 minutes after arrival at the ED. Time point 4: 24 hours after arrival at the ED. Adapted with modifications from Gando et al14 with permission.
8.2 | Late phase

PAI-1 levels, as measured according to activity, antigen levels, and t-PA-PAI-1 complexes, showed persistently high levels after ROSC, for several days after admission to the ED.15,85,86 Elevated PAI-1 levels were significantly higher in non-survivors, patients with unfavorable CPC, and those with multiple organ dysfunction and DIC.85,86 A multiple regression analysis showed that PAI-1 is an independent predictor of increased SOFA scores, especially in patients with DIC.86 This study also showed increases in the levels of both neutrophil elastase and neutrophil-driven fibrin products, especially in DIC patients. Although increased plasmin levels (plasmin-antiplasmin complex) were observed, the results may indicate that t-PA-mediated and neutrophil-mediated fibrinolysis could not overwhelm the PAI-1-induced fibrinolytic shutdown for several days after ROSC, leading to the elevation of SOFA scores, which suggests the development of organ dysfunction.

9 | NO-REFLOW AND MICROVASCULAR THROMBOSIS

9.1 | Animal studies

Fischer and Hossmann demonstrated, in a cat model of cardiac arrest and resuscitation, that an increasing ischemia time was associated with a parallel increase in no-reflow areas in the cerebral cortex and basal ganglia, in which no-flow areas were improved using recombinant t-PA and heparin.87 The reductions of the no-reflow areas were associated with lower plasma TAT levels.88 These results suggest that fibrin microvascular thrombosis is one of the pathomechanisms of cerebral no-reflow after cardiac arrest and resuscitation. Another study clearly showed extensive intravascular clotting in the brain vessels after cardiac arrest and resuscitation in dogs and monkeys.89 Importantly, a prolonged low-flow time due to CPR significantly influenced the cerebral no-flow phenomenon.90 The administration of heparin decreased the mortality rate of the dogs, owing to the formation of large numbers of fibrin clots in the blood after cardiac arrest and resuscitation.9 In addition, rabbits subjected to cardiac arrest and resuscitation showed vascular fibrin thrombus formation in the lungs, spleen, and liver.91 It should be noted that large doses of adrenaline were associated with the formation of microvascular platelets and fibrin thrombi in the heart, spleen, liver, adrenal glands, kidneys and placenta of monkeys in association with decreased platelet counts and plasma fibrinogen levels.10

9.2 | Clinical studies

Two studies confirmed that cortical cerebral blood flow decreased for several hours after cardiac arrest and resuscitation.92,93 The total size of the area of hypoperfusion was larger in patients who remained comatose and died than in those who recovered consciousness.94 Although these studies did not show fibrin thrombosis, the findings in animal studies are indirectly in support of intravascular clotting being due to hypoperfusion in the brain. By examining autopsy records, Hartveit and Halleraker clearly demonstrated microvascular fibrin thrombosis in the glomerular arterioles and capillaries and pulmonary capillaries of nine patients who received CPR but died because of sudden cardiac arrest.95 Two of these nine patients were receiving anticoagulant therapy, which suggests that massive coagulation activation due to systemic ischemia easily exceeds the underlying disease-associated coagulation and fibrinolytic status of patients with cardiac arrest.

10 | DIC AND THE PROGNOSIS OF THE PATIENTS

10.1 | Phenotypes

DIC is always thrombotic, owing to activation of coagulation, insufficient anticoagulation pathways, and inhibition of fibrinolysis by PAI-1.8,80 In some situations, however, the insults that evoke DIC simultaneously release stored t-PA from endothelial Weibel-Palade bodies; this occurs immediately and precedes the induction of PAI-1 mRNA by a couple of hours, and this leads to increased fibrin(gen)olysis98 (Figure 3). It should be noted that the duration of increased fibrinolysis is very short (~3 hours after the insult) and that thrombin generation due to the activation of coagulation and impairment of the anticoagulation pathways always underlies the changes in fibrinolysis. Increased fibrinolysis due to the release of t-PA before expression of PAI-1 mRNA may be called DIC with the fibrinolytic phenotype, which subsequently proceeds to usual thrombotic DIC in patients after cardiac arrest and resuscitation.14,16,77,86,96

10.2 | The prognosis

Increased DIC scores on admission to the ED are associated with inhospital and 6-month death, and an unfavorable long-term neurologic outcome as assessed by the use of CPC scores in patients after cardiac arrest and resuscitation.97,98 Both types of DIC, fibrinolytic77,99 and thrombotic,86 are reported to be associated with multiple organ dysfunction, low survival probability, and a high rate of in-hospital mortality. In addition to DIC scores, both hyperfibrinolysis (defined as fibrin/fibrinogen degradation product [FDP] levels of >100 μg/mL) and fibrinolytic shutdown (assessed by measurement of t-PA-PAI-1 complex levels) were found to be associated with in-hospital death or increased SOFA scores.77,86 These results support the hypothesis that DIC is involved in organ dysfunction and a poor outcome of patients with post-cardiac arrest syndrome.2 In addition, the associations of DIC status, increased DIC scores and FDPs with a poor neurologic outcome were confirmed.78,97,98

Another important point is that, as repeatedly described in the above paragraphs, a long no-flow or low-flow time, both of which indicate prolonged oxygenation impairment after cardiac arrest, affect the development of DIC and the patient’s outcome. A basic study supported this hypothesis by showing that clotting derangement reflecting post-arrest DIC was more severe after longer cardiac...
arrest. Furthermore, precardiac arrest conditions associated with long hypoxic states (e.g., asphyxia, drowning, shock, and exsanguination) are important factors that lead to the development of DIC. This may be one of the reasons for the good prognosis of patients with cardiac arrest of cardiac origin, which can cause immediate ischemia after a very short period of hypoxia (or without hypoxia) during precardiac arrest. Thus, prolonged precardiac arrest hypoxia and long no-flow and low-flow times are considered to be more responsible than the etiologies of cardiac arrest for DIC, through the release of DIC triggers, such as DAMPs, inflammatory cytokines, and adrenaline.

10.3 | Clinical implications

Experimental and clinical studies have failed to prove the beneficial effect of anticoagulants in patients with cardiac arrest and resuscitation. As with anticoagulant therapy for sepsis, patients with post-cardiac arrest syndrome diagnosed with DIC are better therapeutic targets of physiologic anticoagulants, such as antithrombin and recombinant human thrombomodulin, than the entire patient cohort. Therefore, it is important to diagnose DIC properly in patients with cardiac arrest and DIC. These hypotheses should be confirmed in the future.

11 | THE POINT OF THIS REVIEW

This review has confirmed that both cardiac arrest and resuscitation, and sepsis and trauma, elicit the same responses—innate-immune inflammation and coagulation—to maintain homeostasis of the body. If the insults, such as prolonged hypoxia/ischemia in patients with cardiac arrest and resuscitation, are sufficiently severe, then dysregulated responses give rise to organ dysfunction, as described almost three decades ago. DIC associated with SIRS plays a central
role in the dysregulated responses, and is considered to be the main cause of organ dysfunction.4,7,8 This review has also shown that the dysregulated changes in coagulation and fibrinolysis in patients with cardiac arrest and resuscitation meet the ISTH's definition of DIC. Thus, the association of DIC with organ dysfunction and poor outcomes indicates that DIC, rather than simple coagulopathy, is a therapeutic target in patients with post–cardiac arrest syndrome.

12 | CONCLUSIONS

This review has confirmed that patients after cardiac arrest and resuscitation are associated with the following phenomena: (a) triggers of DIC, such as DAMPs, inflammatory cytokines, and catecholamines; (b) platelet activation and exhaustion, with decreased platelet counts; (c) systemic activation of the coagulation system; (d) impairment of the anticoagulation pathways; (e) an increased level of fibrinolysis immediately followed by inhibition of fibrinolysis; (f) neutrophil activation and endothelial injury; and (g) microvascular fibrin thrombosis. All of these phenomena fulfill the definition and have the features of DIC proposed by the SSC on DIC of the ISTH.7 In addition, DIC was associated with multiple organ dysfunction and affected the patient's outcomes, which are the features of DIC, and support the ILCOR Consensus Statement describing increased coagulation as an important cause of multiple organ dysfunction in post–cardiac arrest syndrome.2,7 The studies cited in this review thus support the notion that severe and prolonged hypoxia/ischemia and reperfusion due to cardiac arrest and resuscitation could give rise to DIC, which may affect the outcome of patients with post–cardiac arrest syndrome.

The establishment of therapeutic strategies targeting DIC patients with post–cardiac arrest syndrome is necessary.

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CONFLICT OF INTERESTS

The authors declare no conflicts of interest in relation to the present study.

AUTHOR CONTRIBUTIONS

S. Gando wrote the manuscript. S. Gando and T. Wada contributed evenly to this manuscript through the conception, design, and interpretation and revision of the work. Both authors read and finally approved the work.

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