Jerrold H. Levy, M.D., F.A.H.A., F.C.C.M., Editor

Cardiac Resuscitation and Coagulation

Joseph L. Weidman, M.D., Douglas C. Shook, M.D., Jan N. Hilberath, M.D.

CARDIAC arrest occurs with an estimated annual incidence of 92 to 189 cases per 100,000 individuals and carries a poor prognosis despite advances in modern medicine.[1] Even for patients in whom spontaneous circulation is restored, their subsequent hospital course is fraught with potential complications. Derangements in the coagulation and fibrinolytic systems frequently occur as a result of cardiac arrest and cardiopulmonary resuscitation (CPR). These changes play a significant role in the spectrum of conditions classified as "post–cardiac arrest syndrome."[2] In addition to the endogenous changes in blood coagulation after cardiac arrest, iatrogenic coagulopathies can be seen at various time points as ancillary effects of certain treatment options for these patients (fig. 1).

In this article, we review the changes in the coagulation systems of patients experiencing cardiac arrest and CPR and further discuss coagulopathies potentially associated with hypothermia, thrombolysis, and extracorporeal membrane oxygenation (ECMO) therapy.

Cardiac Arrest and Changes in Endogenous Coagulation and Fibrinolysis

In healthy individuals, equilibrium exists between coagulation and fibrinolysis. After circulatory arrest, this balance is frequently disrupted.

Changes in Endogenous Coagulation and Anticoagulation

Endothelial injury from hypoxemia, lack of organ perfusion, and direct tissue trauma after resuscitation leads to the release of various proinflammatory mediators, whereas levels of counterregulatory, antiinflammatory compounds such as nitric oxide and prostacyclin are significantly depressed.[3] Adrie *et al.*[4] found that interleukin-6 and lactate levels were consistently increased in successfully resuscitated patients with cardiac arrest. In addition, levels of other proinflammatory cytokines such as tumor necrosis factor-α and interleukin-1 were elevated. The abundant activation of multiple pathways of inflammation results in systemic activation of platelets and a secondary release of tissue factor promoting intravascular coagulation through generation of thrombin.[5] This up-regulation of the coagulation cascades is also supported by laboratory evidence of increased levels of thrombin–antithrombin complex, platelet factor-4, fibrin monomers, and thrombin.[4,6] In addition to directly propagating the formation of clot, thrombin possesses potent proinflammatory effects.[7] This reciprocal reinforcement of systemic inflammation and procoagulant activity worsens the thromboembolic complications frequently encountered after cardiac arrest and resuscitation. A significant increase in inflammatory markers in these patients has been associated with higher in-hospital mortality.[4]

In addition to aforementioned procoagulant effects, circulatory arrest and CPR also lead to marked alterations in the body's anticoagulant pathways: Decreased levels of antithrombin, protein C, and protein S can consistently be measured.[4] The activated form of protein C physiologically inhibits thrombin generation, enhances fibrinolysis, and alleviates inflammation thereby promoting a more rapid return to tissue homeostasis. Given these inherent properties, the early decrease in protein C after cardiac arrest may be particularly detrimental in the periresuscitation period.

Changes to the Fibrinolytic System

Acute clot formation is encountered not only in the postresuscitation phase, but it can contribute to the etiology of cardiac arrest in the form of vascular thromboses and systemic embolization. The effective breakdown of thrombus

This article is featured in "This Month in Anesthesiology," page 1A.

Submitted for publication June 7, 2013. Accepted for publication October 25, 2013. From the Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

 Anesthesiology 2014; 120:1009–14

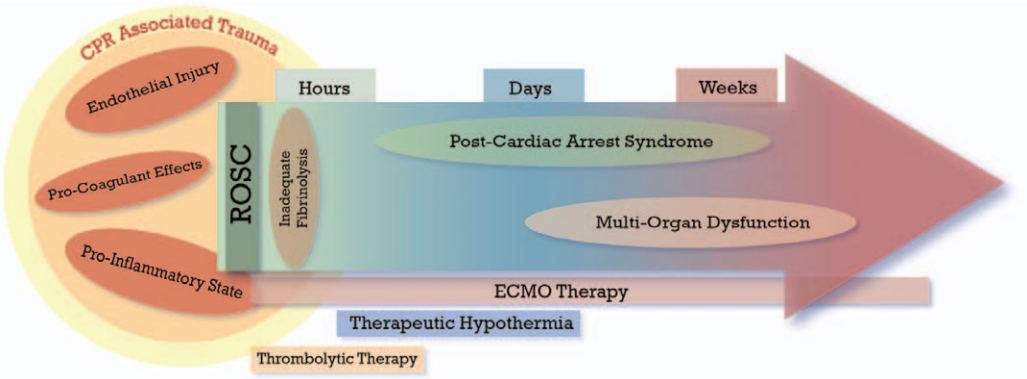

Fig. 1. Time course of coagulation changes in cardiac arrest. Within minutes of circulatory collapse, alterations to the coagulation system can become apparent. Endogenous changes can be further accentuated by therapeutic measures during cardiopulmonary resuscitation (CPR) (*i.e.*, invasive procedures or administration of thrombolytic agents) or by the reperfusion of ischemic tissues. After return of spontaneous circulation (ROSC), iatrogenic factors contributing to coagulopathy become more prominent. The duration of clotting changes from thrombolytic therapy primarily depends on the suspected etiology of cardiac arrest which determines the infusion time (*vs.* bolus administration) of thrombolytics and secondly depends on pharmacologic properties of the selected agent. Coagulopathies associated with therapeutic hypothermia are most relevant during the hours of active cooling and improve with rewarming. Most centers consider the institution of hypothermic treatment no later than 6–12 h after cardiac arrest and continue cooling for 24 h. Extracorporeal membrane oxygenation (ECMO) therapy can be deployed as early as during CPR or after ROSC and is usually carried on for a maximum of up to 30 days depending on healthcare system preferences. Overall, treatment protocols for the care of patients with cardiac arrest remain largely center and resource dependent.

is severely limited after circulatory arrest despite an initial increase in fibrinolytic activity as indicated by mild or moderate increases in D-dimer levels after return of spontaneous circulation. Overall, however, the systemic inflammation and decreased levels of promoters of fibrinolysis (*e.g.*, activated protein C) blunt this physiologic reaction and hinder sufficient fibrinolytic activity.[6] Circulating levels of the direct fibrinolysis inhibitor plasminogen activator inhibitor-1 are also increased after resuscitation. Taken together, these changes represent an inadequate fibrinolytic response relative to the systemic procoagulant state, and this imbalance has been linked to decreased survival after cardiac arrest.[6] A near-total suppression of fibrinolysis after cardiac arrest, as indicated by very low D-dimer levels, is more frequently found in nonsurvivors than in surviving patients.[3]

The body's inability to sufficiently break down clot in the setting of increased systemic thrombus formation is closely related to the pathophysiology of post–cardiac arrest syndrome, and the occurrence of thromboses in the microcirculation contributes to the multiorgan dysfunction frequently witnessed in the postresuscitation period. When vital organs such as brain, lungs, heart, or kidneys are affected, the sequelae for patients can be devastating (figs. 1 and 2).[8]

Coagulopathies Associated with the Treatment of Circulatory Arrest

Management of patients after cardiac arrest is complex, and therapies focus not only on the underlying cause of circulatory arrest but also on the consequences of temporary cessation of organ perfusion and the subsequent resuscitation. Treatment modalities such as therapeutic hypothermia, thrombolysis, and ECMO carry the inherent risk of altering an already deranged coagulation system. Various procedures of advanced cardiac life support such as airway management and vascular or intraosseous cannulations can be traumatic and lead to hemorrhage especially in patients with preexisting coagulopathies.[9] Further bleeding complications can stem from vascular injuries incurred during CPR through chest compressions resulting in rib fractures and injuries to the thoracic vasculature. In addition, gaining large-bore vascular access for the initiation of ECMO therapy or for the institution of invasive therapeutic hypothermia can damage major blood vessels.

Therapeutic Hypothermia

Current treatment guidelines recommend inducing mild hypothermia of 32° to 34°C for 12 to 24 h in comatose patients with return of spontaneous circulation after cardiac arrest as hypothermia provides a neurologic benefit to these patients.[10] Lowering the body temperature decreases the cerebral metabolic rate of oxygen by 6% for every 1°C reduction in brain temperature over 28°C and promotes the preservation of neurologic function. Cooling can improve the microcirculation and prevent formation of microthrombi in the postarrest state.[11] Of note, hypothermia can also be the cause of cardiac arrest rather than a therapeutic measure. In these patients, the degree of hypothermia is usually more severe (<32°C).

Hypothermia is associated with multiple disturbances in the coagulation system, and its anticoagulant effect likely leads to abovementioned improvement in microcirculation.

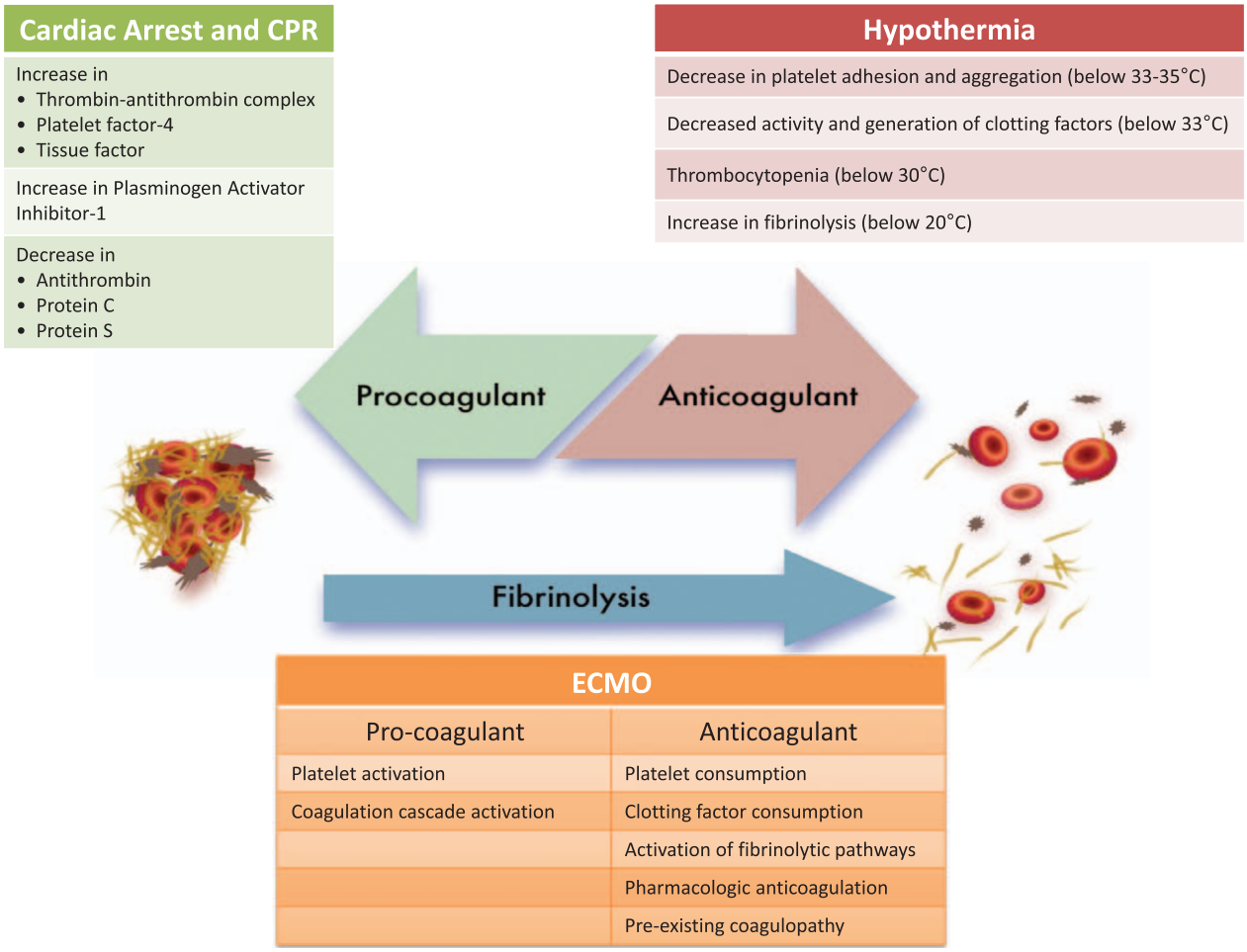

Fig. 2. Impact of cardiac arrest and its treatment options on coagulation. (*Green*) Cardiac arrest and cardiopulmonary resuscitation (CPR) primarily predispose the patient to a procoagulant state with the risk for widespread vascular thromboses. (*Red*) Decreasing temperatures in hypothermia, either as therapeutic measure after return of spontaneous circulation or as underlying cause of cardiac arrest, exponentially inhibit the blood's ability to form clot. (*Orange*) Extracorporeal membrane oxygenation (ECMO) therapy influences the coagulation system in variable ways: The initial abundant activation of clotting factors and platelets through contact with artificial surfaces leads to thromboses and is countered by a potent endogenous anticoagulant response and hyperfibrinolysis. Pharmacologic anticoagulation is necessary to prevent thrombus formation systemically and within the ECMO circuit but is frequently accompanied by bleeding complications.

Hypothermic coagulopathy is the result of a decrease in the function and number of platelets, and a reduction in the enzymatic activity and generation of numerous clotting factors (fig. 2). The correlation between blood temperature and coagulopathy is not linear: the degree of coagulopathy grows exponentially as blood temperature decreases.[12] *In vitro* studies using thromboelastography indicate that this exponential relationship holds true for the time to onset of clot formation (*R* value) as well as for the speed at which the clot achieves firmness (*K* value, α-angle). Once the blood temperature decreases below 16°C, practically no coagulation occurs. Interestingly, low temperatures do not seem to affect clot stability once thrombus formation has been fully achieved.[12]

Hypothermia to 35°C generally has minimal impact on the coagulation system. At temperatures between 32°C to 34°C, changes in coagulation, platelet number, and platelet function may become apparent.[11] The activation process of platelets is not impaired at low temperatures, but platelet dysfunction is the result of decreased adhesion and aggregation that worsens with decreasing temperatures. Below 30°C, a marked decrease in platelet count can be noticed. This hypothermia-related thrombocytopenia is due to cell sequestration, primarily in the liver. Both platelet dysfunction and thrombocytopenia are reversible upon rewarming, and more than 80% of the sequestered platelets return to circulation once normothermia is reestablished.[13] Studies looking at the effect of hypothermia on specific coagulation factors found that enzymatic reactions in the coagulation cascade are only modestly reduced when the blood temperature is lowered from 37° to 33°C, and there was no significant impairment in the overall coagulation process at this mild degree of hypothermia.[14] At temperatures below 33°C, the function of clotting factors central to coagulation starts playing an

increasing role in the genesis of hypothermic coagulopathy. The fibrinolytic pathways seem to be also largely unaffected by mild to moderate degrees of hypothermia.[15] Fibrinolytic activity markedly increased at hypothermia levels below 20°C in animal studies which was attributed to tissue plasminogen activator release from vascular endothelium in response to the rise in circulating catecholamines associated with deep hypothermia.[16]

In a prospective, observational study on adverse events of therapeutic hypothermia after cardiac arrest, bleeding complications requiring transfusions occurred in only 6% of patients and were not associated with increased mortality.[9] If significant bleeding develops during therapeutic hypothermia, practitioners need to weigh the potential benefits of continued hypothermia with the risks of ongoing hemorrhage. As reversible platelet dysfunction is likely the primary cause of coagulopathy at this degree of hypothermia, the first-line treatment is rewarming of the patient.[13] Should continued cooling be considered necessary, various interventions have been explored to improve coagulation in the face of decreased body temperatures: The correction of acidemia is an important early step, as profound acidosis can be seen with hypothermia in certain clinical situations and synergistically impairs coagulation. Moreover, an *in vitro* study using whole blood samples from healthy volunteers found that desmopressin partially corrected the hypothermia-induced coagulopathy by rapidly improving platelet aggregability. This finding is most likely explained by an increased expression of the glycoprotein 1b receptor through redistribution from cytoplasm to the cell membrane. Furthermore, the investigators showed that administration of fibrinogen concentrate assisted in restoring normal coagulation patterns when fibrinogen levels were low as a result of dilution, hypothermia, and acidosis. Both desmopressin and fibrinogen function more effectively at physiologic pH.[17]

Numerous investigations suggest that thrombolytic therapy can be safely used in the setting of therapeutic hypothermia. Patients receiving tissue plasminogen activator during hypothermia treatment had the same incidence of bleeding complications as normothermic patients receiving the medication. However, hypothermic patients who did develop bleeding complications required a greater number of blood transfusions to reach a predefined target hematocrit.[11]

Thrombolysis and Anticoagulant Medications

Investigators have examined the potential role of anticoagulant medications (primarily heparin or aspirin) as well as thrombolytic agents in the immediate treatment of cardiac arrest. Thrombolytics directly degrade thrombus, whereas heparin, in addition to preventing ongoing clot formation, inhibits the actions of plasminogen activator inhibitor-1 and thus allows for a further increase in thrombus degradation by endogenous mechanisms.[18] In their meta-analysis, Li *et al.*[19] reviewed eight studies comparing the outcomes of patients with cardiac arrest treated with thrombolytics and heparin during CPR. The study concluded that return of spontaneous circulation, 24 h survival, survival to hospital discharge, and long-term neurologic function were all improved in the treatment groups. To further investigate the potential benefit of thrombolysis in cardiac arrest in a prospective multicenter, randomized study, the Thrombolysis during Resuscitation for Out-of-Hospital Cardiac Arrest (TROICA) trial was undertaken in Europe.[20] Patients suffering from out-of-hospital cardiac arrest were randomized to receive either tenecteplase or placebo at the time of CPR. This trial was prematurely suspended after a formal futility analysis for primary and secondary endpoints revealed no differences in patient outcomes between intervention and placebo and the incidence of intracranial hemorrhage was significantly higher in the tenecteplase group. As the data currently stand, thrombolytic therapy should not be used routinely in the treatment of cardiac arrest. Only when massive pulmonary embolism is suspected to be the cause of cardiac arrest or if the primary pathologic condition is known to be responsive to such treatment, thrombolysis appears reasonable.[21]

The use of anticoagulant medications during cardiac arrest and CPR makes bleeding complications more likely. This can become apparent in patients receiving antiplatelet and anticoagulant therapy in whom myocardial ischemia or infarction is suspected as underlying causes of circulatory collapse. The recent, more widespread use of novel oral anticoagulants in patients with preexisting heart disease and their impact on the bleeding diathesis after cardiac arrest are causes for great concern and have not been studied to date. Significant difficulties in reversing the anticoagulant effects of these drugs have been reported in other clinical settings.

ECMO

Extracorporeal membrane oxygenation is a successful means to improve oxygenation and deliver blood flow to vital organs, but it is not without its share of potential side effects. Relatively common complications are bleeding and thrombosis, both of which can be life threatening. Epidemiologic data indicate that the usage of veno-arterial ECMO in refractory cardiac arrest and CPR is increasing. Although further research is needed, outcome data seem promising and survival rates average in the literature approximately 30%. A recent single-center, prospective study showed a 50% increase in 1-yr survival after in-hospital cardiac arrest for patients treated with ECMO.[22]

Exposure of a patient's blood to the nonbiologic surfaces of an extracorporeal circuit results in a considerable inflammatory and coagulation response. Almost immediately after ECMO initiation, platelets adhere to the surface of the tubing and release α-granules leading to the activation and aggregation of additional platelets. The foreign material of the circuit also activates numerous procoagulant factors of the coagulation cascade and platelet granules reinforce this increase in factor activity. As a result, thrombin is generated and stimulates further platelet activation *via* a positive feedback loop.

This uncontrolled activation of the coagulation system triggers the up-regulation of the fibrinolytic system in response. Together, the release of coagulation factors through surface contact, the abundant activation of the complement system, and the intense inflammatory response causing degranulation of granulocytes fuel the procoagulant as well as fibrinolytic and anticoagulant processes.[23] This results in a net loss of platelets, consumption of clotting factors, and the formation of widespread thrombi. Clot within the ECMO circuit is the most imminently harmful consequence as it can result in malfunction of the oxygenator, obstruction of blood flow, or systemic embolization to the brain and other vital organs. Heparin is the most common anticoagulant used to mitigate this reaction but inherently increases the risk of bleeding, especially with increasing duration of ECMO therapy.[24] Although heparin has little direct influence on platelet activity, it effectively limits thrombus formation through inhibition of various reactions in the coagulation cascade. Its effectiveness against clot formation appears to diminish as the duration of ECMO therapy increases. Thus, finding a balance between excessive and inadequate levels of anticoagulation is a critical element of ECMO management (fig. 2).

Monitoring of Coagulation in Cardiac Arrest and Resuscitation

As coagulopathies and bleeding complications are common after cardiac arrest and resuscitation, routine monitoring of coagulation parameters should be used. Laboratory studies including platelet count, prothrombin time, activated partial thromboplastin time, and measurement of fibrinogen levels can help to specify various coagulation abnormalities. A careful patient evaluation and their medical as well as medication history can uncover preexisting hematologic or pharmacologic causes of abnormal hemostasis. Treatment plans should focus on the specific underlying coagulation defects and fresh-frozen plasma or factor concentrates may be used to replace factor deficiencies if indicated. Fibrinogen levels can be independently maintained in the physiologic range through administration of either cryoprecipitate or fibrinogen concentrates where available. Ultimately, the clinician's decision to transfuse blood products or specific factor concentrates in these patients will be dictated by the necessity to treat hemorrhagic complications, not by the presence of isolated, abnormal laboratory values.

In patients on ECMO therapy, activated clotting time is the laboratory test predominantly used to manage the necessary anticoagulation and it is measured in samples of whole blood. Activated clotting time is not a specific test for anticoagulants, and a prolonged value can be the result of deficiencies in various steps of the coagulation cascade. In fact, some data suggest that heparin dosing based on direct measurement of blood heparin levels rather than activated clotting time results in favorable outcomes.[24] In some centers, activated partial thromboplastin time has become the test of choice for anticoagulation monitoring in ECMO patients as it reflects a universally recognized laboratory standard. For heparin anticoagulation within the usual target range, activated partial thromboplastin time can present a reasonable alternative to activated clotting time during ECMO. Finally, thromboelastography has been proposed as a measure of anticoagulation in these patients. To date, the management of anticoagulation and hemorrhage on ECMO is lacking steadfast guidelines and remains largely center dependent. Correcting thrombocytopenia through platelet transfusions has been linked to decreased overall bleeding complications in ECMO patients, and therefore regular measurements of platelet count are warranted during therapy.[23] Available clinical practice guidelines suggest a possible benefit of antifibrinolytic agents such as aminocaproic acid or tranexamic acid in the prevention of bleeding in ECMO patients. In addition, recombinant factor VIIa might prove useful when faced with situations of life-threatening hemorrhage, but the potential advantages need to be carefully considered against the possibility of catastrophic thrombotic complications.[25]

Conclusions

Healthcare professionals caring for patients in the setting of cardiac arrest and CPR commonly encounter significant disruptions in blood coagulation. These coagulopathies are typically multifactorial and represent a combination of endogenous and iatrogenic components. Understanding the various underlying mechanisms and recognizing the respective treatment options can greatly enhance patient care and will hopefully further improve outcomes.

Acknowledgments

The authors thank Samuel Rodriguez, M.D., Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital, Boston, Massachusetts, for providing significant help with the illustrations.

Support was provided solely from institutional and/or departmental sources.

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Hilberath: Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, Massachusetts 02115. jhilberath@partners.org.

References

1. Holzer M: Targeted temperature management for comatose survivors of cardiac arrest. N Engl J Med 2010; 363:1256–64
2. Nolan JP, Neumar RW, Adrie C, Aibiki M, Berg RA, Böttiger BW, Callaway C, Clark RS, Geocadin RG, Jauch EC, Kern KB, Laurent I, Longstreth WT, Merchant RM, Morley P,

Morrison LJ, Nadkarni V, Peberdy MA, Rivers EP, Rodriguez-Nunez A, Sellke FW, Spaulding C, Sunde K, Hoek TV: Post-cardiac arrest syndrome: Epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke. Resuscitation 2008; 79:350–79

3. Kleinman ME, Srinivasan V: Postresuscitation care. Pediatr Clin North Am 2008; 55:943–67, xi
4. Adrie C, Monchi M, Laurent I, Um S, Yan SB, Thuong M, Cariou A, Charpentier J, Dhainaut JF: Coagulopathy after successful cardiopulmonary resuscitation following cardiac arrest: Implication of the protein C anticoagulant pathway. J Am Coll Cardiol 2005; 46:21–8
5. Gando S, Nanzaki S, Morimoto Y, Kobayashi S, Kemmotsu O: Tissue factor and tissue factor pathway inhibitor levels during and after cardiopulmonary resuscitation. Thromb Res 1999; 96:107–13
6. Böttiger BW, Motsch J, Böhrer H, Böker T, Aulmann M, Nawroth PP, Martin E: Activation of blood coagulation after cardiac arrest is not balanced adequately by activation of endogenous fibrinolysis. Circulation 1995; 92:2572–8
7. Esmon CT: Protein C anticoagulant pathway and its role in controlling microvascular thrombosis and inflammation. Crit Care Med 2001; 29(7 suppl):S48–51
8. Mysiak A, Nowicki P, Kobusiak-Prokopowicz M: Thrombolysis during cardiopulmonary resuscitation. Cardiol J 2007; 14:24–8
9. Nielsen N, Sunde K, Hovdenes J, Riker RR, Rubertsson S, Stammet P, Nilsson F, Friberg H; Hypothermia Network: Adverse events and their relation to mortality in out-of-hospital cardiac arrest patients treated with therapeutic hypothermia. Crit Care Med 2011; 39:57–4
10. Hazinski MF, Nolan JP, Billi JE, Böttiger BW, Bossaert L, de Caen AR, Deakin CD, Drajer S, Eigel B, Hickey RW, Jacobs I, Kleinman ME, Kloeck W, Koster RW, Lim SH, Mancini ME, Montgomery WH, Morley PT, Morrison LJ, Nadkarni VM, O'Connor RE, Okada K, Perlman JM, Sayre MR, Shuster M, Soar J, Sunde K, Travers AH, Wyllie J, Zideman D: Part 1: Executive summary: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation 2010; 122(16 suppl 2):S250–75
11. Polderman KH: Mechanisms of action, physiological effects, and complications of hypothermia. Crit Care Med 2009; 37(7 suppl):S186–202
12. Ruzicka J, Stengl M, Bolek L, Benes J, Matejovic M, Krouzecky A: Hypothermic anticoagulation: Testing individual responses to graded severe hypothermia with thromboelastography. Blood Coagul Fibrinolysis 2012; 23:285–9
13. Michelson AD, MacGregor H, Barnard MR, Kestin AS, Rohrer MJ, Valeri CR: Reversible inhibition of human platelet activation by hypothermia *in vivo* and *in vitro*. Thromb Haemost 1994; 71:633–40
14. Wolberg AS, Meng ZH, Monroe DM III, Hoffman M: A systematic evaluation of the effect of temperature on coagulation enzyme activity and platelet function. J Trauma 2004; 56:1221–8
15. Watts DD, Trask A, Soeken K, Perdue P, Dols S, Kaufmann C: Hypothermic coagulopathy in trauma: Effect of varying levels of hypothermia on enzyme speed, platelet function, and fibrinolytic activity. J Trauma 1998; 44:846–54
16. Yoshihara H, Yamamoto T, Mihara H: Changes in coagulation and fibrinolysis occurring in dogs during hypothermia. Thromb Res 1985; 37:503–12
17. Hanke AA, Dellweg C, Schöchl H, Weber CF, Jüttner B, Johanning K, Görlinger K, Rahe-Meyer N, Kienbaum P: Potential of whole blood coagulation reconstitution by desmopressin and fibrinogen under conditions of hypothermia and acidosis—An *in vitro* study using rotation thrombelastometry. Scand J Clin Lab Invest 2011; 71:292–8
18. Patston PA, Schapira M: Low-affinity heparin stimulates the inactivation of plasminogen activator inhibitor-1 by thrombin. Blood 1994; 84:1164–72
19. Li X, Fu QL, Jing XL, Li YJ, Zhan H, Ma ZF, Liao XX: A meta-analysis of cardiopulmonary resuscitation with and without the administration of thrombolytic agents. Resuscitation 2006; 70:31–6
20. Böttiger BW, Arntz HR, Chamberlain DA, Bluhmki E, Belmans A, Danays T, Carli PA, Adgey JA, Bode C, Wenzel V; TROICA Trial Investigators; European Resuscitation Council Study Group: Thrombolysis during resuscitation for out-of-hospital cardiac arrest. N Engl J Med 2008; 359:2651–62
21. Jaff MR, McMurtry MS, Archer SL, Cushman M, Goldenberg N, Goldhaber SZ, Jenkins JS, Kline JA, Michaels AD, Thistlethwaite P, Vedantham S, White RJ, Zierler BK; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; American Heart Association Council on Peripheral Vascular Disease; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology: Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: A scientific statement from the American Heart Association. Circulation 2011; 123:1788–830
22. Chen YS, Lin JW, Yu HY, Ko WJ, Jerng JS, Chang WT, Chen WJ, Huang SC, Chi NH, Wang CH, Chen LC, Tsai PR, Wang SS, Hwang JJ, Lin FY: Cardiopulmonary resuscitation with assisted extracorporeal life-support *versus* conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: An observational study and propensity analysis. Lancet 2008; 372:554–61
23. Muntean W: Coagulation and anticoagulation in extracorporeal membrane oxygenation. Artif Organs 1999; 23:979–83
24. Baird CW, Zurakowski D, Robinson B, Gandhi S, Burdis-Koch L, Tamblyn J, Munoz R, Fortich K, Pigula FA: Anticoagulation and pediatric extracorporeal membrane oxygenation: Impact of activated clotting time and heparin dose on survival. Ann Thorac Surg 2007; 83:912–9
25. Ferraris VA, Brown JR, Despotis GJ, Hammon JW, Reece TB, Saha SP, Song HK, Clough ER, Shore-Lesserson LJ, Goodnough LT, Mazer CD, Shander A, Stafford-Smith M, Waters J, Baker RA, Dickinson TA, FitzGerald DJ, Likosky DS, Shann KG: 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg 2011; 91:944–82