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FORUM

Shock, acute disseminated intravascular coagulation, and microvascular thrombosis: is 'shock liver' the unrecognized provocateur of ischemic limb necrosis?

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Summary. For unknown reasons, a small minority of critically ill patients with septic or cardiogenic shock, multiorgan failure, and disseminated intravascular coagulation develop symmetrical acral (distal extremity) limb loss due to microvascular thrombosis ('limb gangrene with pulses'). Case reports have described preceding 'shock liver' in some critically ill patients who developed such a picture of ischemic limb necrosis. This suggests that profoundly disturbed procoagulant–anticoagulant balance featuring uncontrolled generation of thrombin—resulting from failure of the protein C and antithrombin natural anticoagulant systems due to insufficient hepatic synthesis of these crucial proteins—could explain the microvascular thrombosis and associated limb loss. We hypothesize that shock liver is the key predisposing risk factor underlying ischemic limb necrosis in the majority of patients who develop this complication in the setting of acute disseminated intravascular coagulation complicating septic or cardiogenic shock. As shock liver precedes onset of limb ischemia by several days, therapeutic intervention may be possible.

Keywords: antithrombin III; disseminated intravascular coagulation; gangrene; liver failure, acute; protein C.

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Introduction

Ischemic limb necrosis complicating disseminated intravascular coagulation (DIC) is rare. It occurs in a minority of patients with DIC, usually in the setting of critical illness secondary to septicemia or cardiogenic shock [1,2]. Four recent case reports have described preceding hypoxic liver injury (also known as 'shock liver') in patients who subsequently developed distal extremity necrosis associated with acute DIC [3–6]. We hypothesize that acute hepatic dysfunction, which results in reduced synthesis of two crucial hepatically synthesized natural anticoagulants (protein C and antithrombin), predisposes to microvascular thrombosis—and ischemic limb necrosis—in DIC. We find parallels with another syndrome characterized by profoundly disturbed procoagulant–anticoagulant balance, namely warfarin- (coumarin-) associated venous limb gangrene in the setting of acute hypercoagulability states, such as heparin-induced thrombocytopenia [7] and cancer-associated DIC [8]. In essence, we posit that shock liver represents a 'coumarin equivalent' in predisposing to natural anticoagulant depletion and associated microthrombosis underlying ischemic limb loss.

Microvascular thrombosis and ischemic limb loss

Limb necrosis in the setting of septic or cardiogenic shock is characterized by peripheral gangrene of the distal limbs that typically exhibits a glove-and-stocking distribution ('symmetrical peripheral gangrene') [1,2,6]. Arterial pulses, identifiable through palpation and/or Doppler ultrasound, are usually present, and there is an absence of large vessel occlusion or vasculitis; rather, microthrombi in capillaries and postcapillary venules are the predominant pathological finding [9–11]. Some authors have attributed limb necrosis to vasopressor use in critically ill patients with profound hypotension [12]. However, although both hypotension and resulting vasopressor use are common in critically ill patients, limb necrosis is not. We believe that vasopressors—by compromising acral limb flow—predis-

pose to microvascular thrombosis relating to uncontrolled DIC, much like sluggish blood flow secondary to deep vein thrombosis predisposes to ipsilateral acral ischemic limb necrosis in patients with warfarin-associated venous limb gangrene [13,14]. However, hypotension and/or vasopressor use is not the driving factor of 'gangrene with pulses' in the setting of shock. Figure 1 (leftmost portion) summarizes the clinical picture.

Liver dysfunction and natural anticoagulant depletion: a shocking hypothesis

Shock liver—also known as 'hypoxic hepatitis' and 'hypoxic liver injury'—is characterized by an abrupt increase in serum aminotransferase levels. This increase is usually at least 20× the upper limit of normal and typically reaches peak levels 1–3 days after an episode of hypotension [15]. Mortality is > 50%, but complete resolution of hepatic function typically occurs in survivors. The liver synthesizes both procoagulant and anticoagulant factors: a key concept is that procoagulant processes can continue apace even as consumption and depletion of procoagulant factors occur [4]. However, the ability to downregulate and thereby control microvascular thrombosis is compromised if levels of the natural anticoagulants, protein C and antithrombin, are critically reduced.

This precise picture of profoundly impaired procoagulant–anticoagulant balance was observed in a patient with acute DIC and hypoxic liver injury complicating cardiogenic shock: at the onset of limb necrosis, procoagulant markers such as fibrin monomer, fibrin D-dimer, and thrombin–antithrombin complexes were elevated 200- to 300-fold, whereas levels of protein C and antithrombin were profoundly reduced (1% and 20% of normal, respectively) [4]. A more recently reported patient case of ischemic limb necrosis associated with acute DIC and preceding shock liver [6] noted nearly 100-fold increased levels of fibrin monomer and D-dimer, along with severely reduced levels of protein C and antithrombin (1% and 32% of normal, respectively).

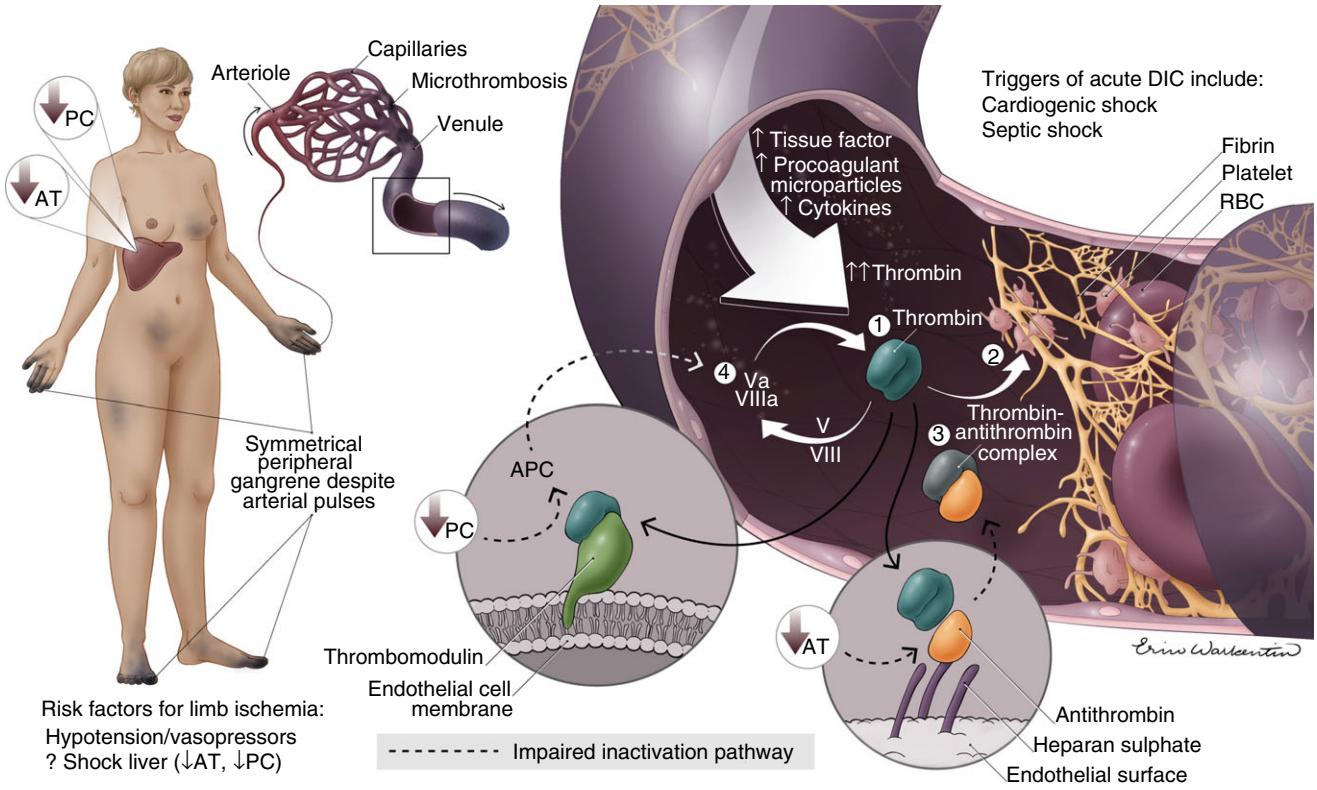

Fig. 1. The role of shock liver in explaining microvascular thrombosis and resulting limb ischemic necrosis ('symmetrical peripheral gangrene') in acute disseminated intravascular coagulation (DIC). Shock liver results in reduced synthesis of two natural anticoagulants: protein C (PC) and antithrombin (AT). Thrombin generation is greatly increased in acute DIC caused by cardiogenic and septic shock, as a result of increased production of tissue factor and proinflammatory cytokines, and formation of procoagulant platelet-derived microparticles. Thrombin (1) enhances its own feedback (by activating factors V (FV) and FVIII to FVa and FVIIIa, respectively, and (2) triggers formation of fibrin-rich thrombi by converting fibrinogen into fibrin. Thrombin is inactivated by (3) covalent binding to antithrombin (forming thrombin–antithrombin complexes), a process enhanced by endothelial heparan sulfate (or pharmacological heparin). Finally, thrombin binds to endothelium-bound thrombomodulin, where it activates PC to activated protein C (APC); (4) APC inactivates FVa and FVIIIa, resulting in downregulation of thrombin generation. Thus, greatly reduced AT and PC production in shock liver predisposes to microthrombosis, which is exacerbated by risk factors for reduced blood flow into the extremities (hypotension, vasopressors). RBC, red blood cell.

A drastic reduction in antithrombin and protein C production as a result of hepatic dysfunction—combined with increased factor consumption secondary to DIC—is the proposed link between shock liver, microthrombosis, and ischemic limb necrosis in the setting of acute DIC. Antithrombin (formerly known as antithrombin III) is an important physiological regulator of thrombin. In the presence of endogenous endothelium-bound glycosaminoglycans or (pharmacologic) heparin, antithrombin forms covalent complexes with thrombin. The thrombin–antithrombin complex results in irreversibly inactivated thrombin [16].

Thrombin bound to endothelial-bound thrombomodulin activates protein C, which in turn inactivates factors Va (FVa) and FVIIIa. This leads to downregulation of thrombin generation [17]. The endothelium-dependent activation of protein C explains why failure of the protein C natural anticoagulant system in shock liver results in microvascular thrombosis; the ratio of endothelial surface area to blood volume is greatest in the smallest blood vessels [17]. The microvasculature is thus most prone to diffuse thrombosis when the procoagulant–anticoagulant balance is greatly disturbed. Indeed, severely reduced protein C levels have been implicated in the pathogenesis of purpura fulminans and resulting ischemic limb loss in patients with meningococcemia [18,19] (and our hypothesis would also predict that concomitant shock liver could be an unrecognized risk factor in these patients as well). Figure 1 (rightmost portion) summarizes the pathophysiological picture.

Support for our hypothesis that severe concomitant antithrombin and protein C depletion contributes to limb necrosis can be found in a 2013 publication [20] that described a mouse model in which RNA interference was used to 'knock down' antithrombin (*Serpinc1*) and/or protein C (*Proc*) genes. Silencing both genes resulted in tissue fibrin deposition and, in some cases, murine hindlimb ischemia. This was not observed if only antithrombin or protein C production was suppressed.

Further evidence supporting our hypothesis includes retrospective observations made by one of us (T.E.W.); among 15 patients with symmetrical peripheral gangrene complicating cardiogenic or septic shock, 14 (93%) had preceding shock liver that began between 2 and 5 days before the onset of limb ischemia [21], an interval reminiscent of coumarin necrosis.

Clinical and pathophysiological parallels with coumarin necrosis

Microvascular thrombosis also underlies acral and non-acral skin necrosis syndromes in patients with coumarin necrosis [14]. In this syndrome, levels of protein C (a vitamin K–dependent factor) are reduced secondary to therapy with vitamin K antagonists like warfarin. Associated acute hypercoagulability leads to thrombosis in the smallest blood vessels leading to dermal/subdermal necrosis. The potential importance of combined depletion of protein C and antithrombin is inferred by reports indicating that warfarin-associated skin necrosis can also occur in patients with congenital antithrombin deficiency [22,23].

The putative 'acute DIC/hepatic necrosis-limb necrosis syndrome' has several parallels with warfarin-associated venous limb gangrene, which complicates hypercoagulability states such as heparin-induced thrombocytopenia and cancer-associated DIC [7,8]. Both disorders are characterized by marked increase in thrombin generation, as shown by greatly elevated thrombin–antithrombin complexes [4,7,8]. Both have localizing factors that predispose to limb loss: in venous limb gangrene, microvascular thrombosis occurs in the limbs with established deep vein thrombosis, whereas in patients with acute DIC and shock liver, hypotension and vasopressor use predispose to acral ischemic necrosis. Both have a characteristic timing of onset: warfarin-associated necrosis begins 2–5 days after initiating warfarin therapy (it takes several days for protein C levels to reach critically low levels), and similarly, onset of ischemic limb necrosis has been observed to begin 2–5 days after the onset of shock liver [3–6]. In both disorders, greatly reduced protein C levels likely play a key role. Yet, unlike warfarin-associated venous limb gangrene—where primarily the protein C natural anticoagulant system is disturbed—with shock liver, both the antithrombin and protein C natural anticoagulant systems can become severely compromised [4,6].

In recent years, it has become recognized that the coagulopathy of chronic liver disease presents a largely 'balanced' reduction of procoagulant and anticoagulant factors, thereby explaining why patients with abnormal coagulation tests (such as international normalized ratio and activated partial thromboplastin time) may not necessarily have a bleeding (or thrombotic) diathesis despite their coagulopathy [24,25]. Here, again, insights from warfarin-induced venous limb gangrene are instructive: Warfarin, too, causes a balanced reduction in both procoagulant and anticoagulant factors, yet in the aforementioned scenarios of *acute* hypercoagulability states such as heparin-induced thrombocytopenia and cancer, warfarin paradoxically exerts a net procoagulant effect, as the ability to downregulate pathological thrombin generation is lost [6–8]. Support for a parallel concept of *chronic* liver disease also representing a high-risk scenario for microthrombosis during a superimposed *acute* hypercoagulable state includes a recently reported patient case [26] of a woman with chronic alcohol-associated liver disease who presented with a relatively balanced reduction of procoagulant and anticoagulant hemostatic factors. Nevertheless, because she developed severe acute DIC associated with *Klebsiella* pneumosepsis, retiform purpura followed by lower- and upper-limb ischemic necrosis developed, along with laboratory evidence of profoundly disturbed procoagulant–anticoagulant balance (fibrin

D-dimer > 20 000 mg L^{-1} fibrinogen equivalent units; protein C and antithrombin levels, 20% and 24%, respectively) [26].

Hypothesis testing

To understand how liver function, protein C, and antithrombin levels change in the setting of critical illness and shock, a prospective cohort study of this patient population could be conducted, with comparisons made between patients who develop concomitant shock liver and those who do not. Further, the hypothesis that shock liver accounts for microvascular thrombosis and ischemic limb necrosis in DIC could be evaluated by a case-control study. This study design is a pragmatic way to explore potential causal factors for rare phenomena. A series of cases—critically ill patients who developed ischemic limb loss—could be systematically gathered in a retrospective review of medical records. Controls—critically ill patients without ischemic limb loss—would then be matched to the cases, for demographics, preexisting conditions, vasopressor use, APACHE score, underlying cause of shock, and other key prognostic factors. We predict that the frequency of shock liver would be markedly greater in the former group of patients with ischemic limb loss. Although multiorgan failure in hypotensive, vasopressor-dependent critically ill patients is a common clinical scenario, our hypothesis specifically predicts that the minority who evince both acute DIC and concomitant shock liver are at highest risk of developing microvascular thrombosis due to a perfect storm of profoundly disturbed procoagulant–anticoagulant balance.

The syndrome of shock liver and venous limb gangrene is a rare and highly morbid condition. Multicenter collaboration would facilitate further study into its diagnosis and treatment. To that end, we propose the creation of an international web-based registry to collect information on affected patients.

Treatment implications

Vitamin K is recommended for patients diagnosed with heparin-induced thrombocytopenia who are receiving warfarin, and its timely administration can prevent the subsequent development of warfarin-induced venous limb gangrene [27]. Analogously, the observation that shock liver in patients with acute DIC precedes onset of ischemic limb necrosis by a few days suggests a possible therapeutic window in which microthrombosis—and associated limb loss—might be preventable. Our current approach is a combination of anticoagulation with unfractionated heparin (using anti-FXa levels to guide dosing, as the activated partial thromboplastin time is often elevated in patients with DIC) and administering frozen plasma (to provide a balance of procoagulant and anticoagulant factors). Although protein C and antithrombin concentrates could be administered, the former are difficult to obtain for an off-label indication, and the latter have never been proved in randomized trials to influence the course of DIC [28]. However, our hypothesis does suggest that antithrombin concentrates might benefit the subset of patients at risk for ischemic limb gangrene in the setting of shock liver and severe antithrombin depletion. In contrast, endothelial dysfunction in certain DIC states such as septicemia could prevent therapeutic benefit of protein C administered through frozen plasma infusion (e.g., if shedding of endothelial thrombomodulin has occurred) [29]. Such considerations indicate an important potential role for treatment with recombinant human soluble thrombomodulin, which is currently undergoing clinical evaluation in patients with severe sepsis [30].

Addendum

T. E. Warkentin first proposed the hypothesis, and M. Pai helped to develop it and to propose studies in order to test it.

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Disclosure of Conflict of Interests

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