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Fisiopatologia applicata alla medicina critica

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Gravi emorragie post-traumatiche

Curry *et al. Critical Care* 2011, **15**:R92
http://ccforum.com/content/15/2/R92

CRITICAL CARE

RESEARCH Open Access

The acute management of trauma hemorrhage: a systematic review of randomized controlled trials

Nicola Curry[1*], Sally Hopewell[2,3], Carolyn Dorée[2], Chris Hyde[4], Karim Brohi[5], Simon Stanworth[1]

Haemorrhage is responsible for up to 40% of trauma deaths.
A systematic review of RCTs which evaluated trauma patients with hemorrhagic shock within the first 24 hours of injury.

Conclusions: Despite 35 RCTs there has been little improvement in outcomes over the last few decades.

Concezione tradizionale della genesi della “coagulopatia da trauma”

Numerosi fattori concatenati:

Danno dei tessuti
Emorragia
Ipoperfusione tessutale
Acidosi
Somministrazione di liquidi (colloidi o cristalloidi)
Emodiluizione (riduzione fattori coag., piastrinopenia)
Ipotermia (ridotta attività processi coagulativi)
Infiammazione

A new vision on pathogenesis of coagulopathy in severely injured pts
(Brohi, Ann Surg 2007)

It was commonly believed that any hypocoagulable state after trauma was due to iatrogenic mechanisms:

hypothermia, dilution and metabolic acidosis that resulted from resuscitation and surgical care

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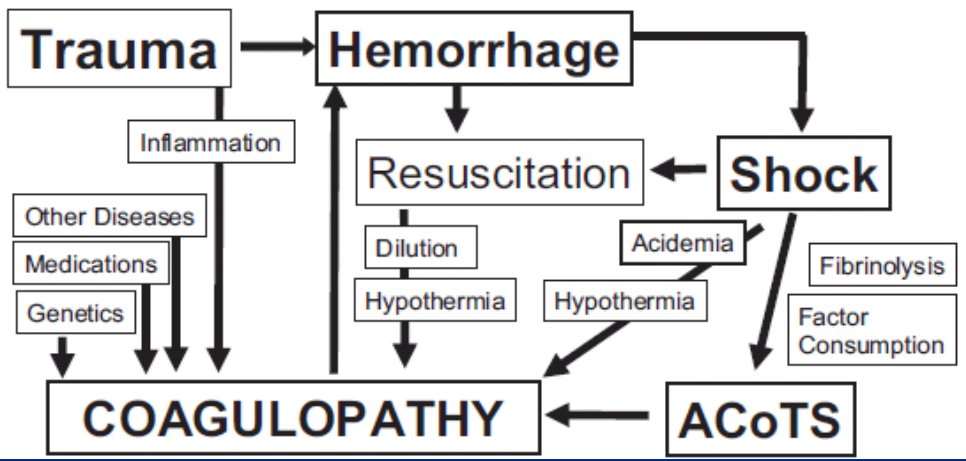
Coagulopathy however can take place before significant resuscitation, dilution and hypothermia (detected in 30% of pts after 1 h from trauma).

The Coagulopathy of Trauma: A Review of Mechanisms

Hess et al., J Trauma 2008



Trauma leads to hemorrhage which can lead to resuscitation, which in turn leads to dilution and hypothermia causing coagulopathy and further hemorrhage. Hemorrhage can also cause shock which causes acidosis and hypothermia that in turn lead to coagulopathy, the "fatal triad".

Acute coagulopathy of trauma: mechanism, identification and effect

Karim Brohi[a], Mitchell J. Cohen[b] and Ross A. Davenport[a]

Curr Opin Crit Care 2007

Summary of studies of acute coagulopathy of trauma

	Definition of coagulopathy	Number of patients	Percentage with coagulopathy	Mortality coagulopathy
Brohi, 2003 [6]	PT >18 s or PTT >60 s	1088	24%	46%
MacLeod, 2003 [7]	PT >14 s or PTT >35 s	10 790	28%	19%
Maegele, 2007 [8•]	Quick test <70%	8724	34%	28%
Brohi, 2007 [9••]	PT >18 s or PTT >60 s[c]	208	10%	62%
Rugeri, 2007 [10•]	INR > 1.6 or PTT >60 s	88	28%	n/a

- Acute coagulopathy of trauma occurs in patients with shock and is characterized by a systemic anticoagulation and hyperfibrinolysis.

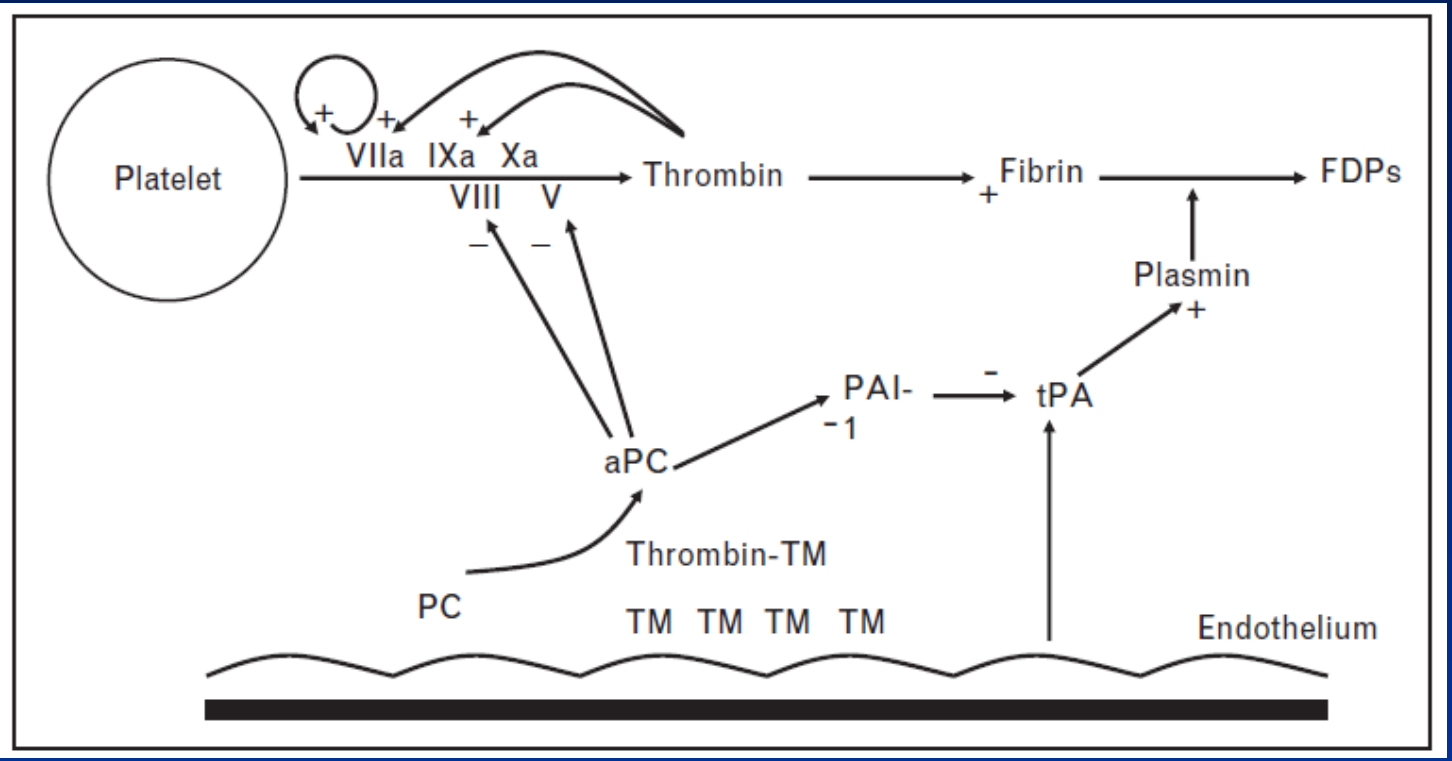
- Dilution, acidemia and consumption of coagulation proteases do not appear to be significant factors at this stage.

Mechanism of acute coagulopathy in trauma

Instead of being a dysfunction of the coagulation proteases, acute coagulopathy appears to be due to activation of anticoagulant and fibrinolytic pathways.

The thrombomodulin–protein C pathway is implicated in these processes.

Activation of PC by thrombin (activation of coagulation) and thrombomodulin (released from endothelium injured by hypoperfusion) With subsequent anticoagulant and pro-fibrinolytic effects of activated PC



From Brohi et al., Curr Opin Crit Care 2007

Trauma and fibrinolysis

- Trauma is associated with increased fibrinolytic activity
- Activation of fibrinolysis occurs as tPA is released from the endothelium following injury and ischemia
- Activated protein C in excess will consume PAI-1, thus leading to increased fibrinolytic activity
- As a result, D-dimer levels are highly increased

Critical Role of Activated Protein C in Early Coagulopathy and Later Organ Failure, Infection and Death in Trauma Patients

by Cohen et al., Ann Surg 2012

- 203 patients with tissue hypoperfusion and severe traumatic injury
- strong activation of the PC
- coagulopathy = inactivation F V and VIII and hyperfibrinolysis with high levels of tPA and D-dimers

- High levels of activated PC were associated with increased mortality, organ injury, > blood transfusion
- Finally early depletion of PC after trauma is associated with posttraumatic ventilator-associated pneumonia.

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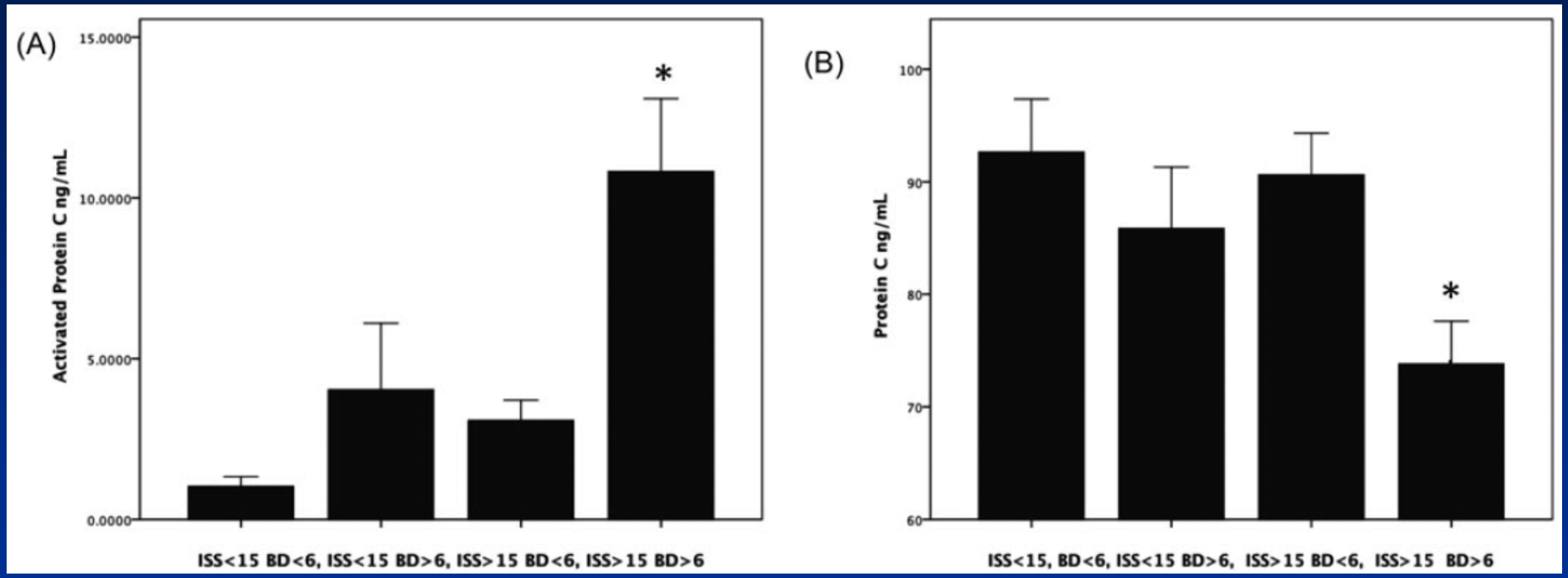

Patients divided in 4 groups using Injury Severity Score and Shock based on Base Deficit.

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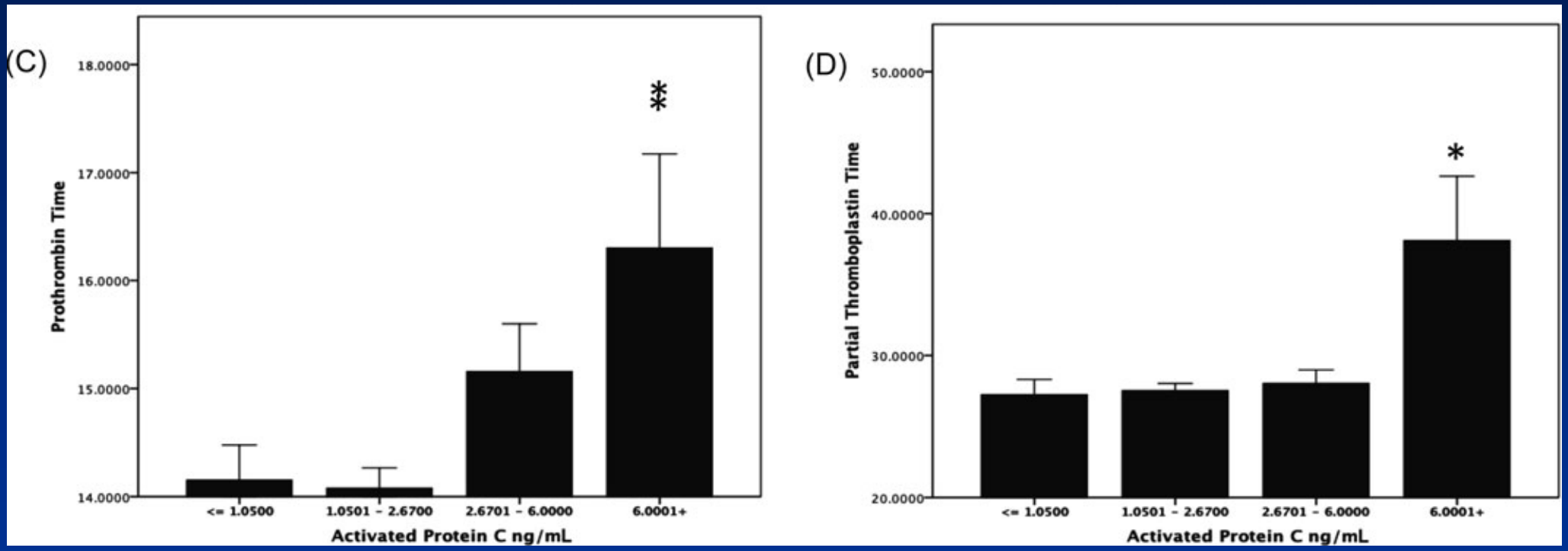
by Cohen et al., Ann Surg 2012



Prolongation of PT and aPTT in the 4 quartiles of activated PC

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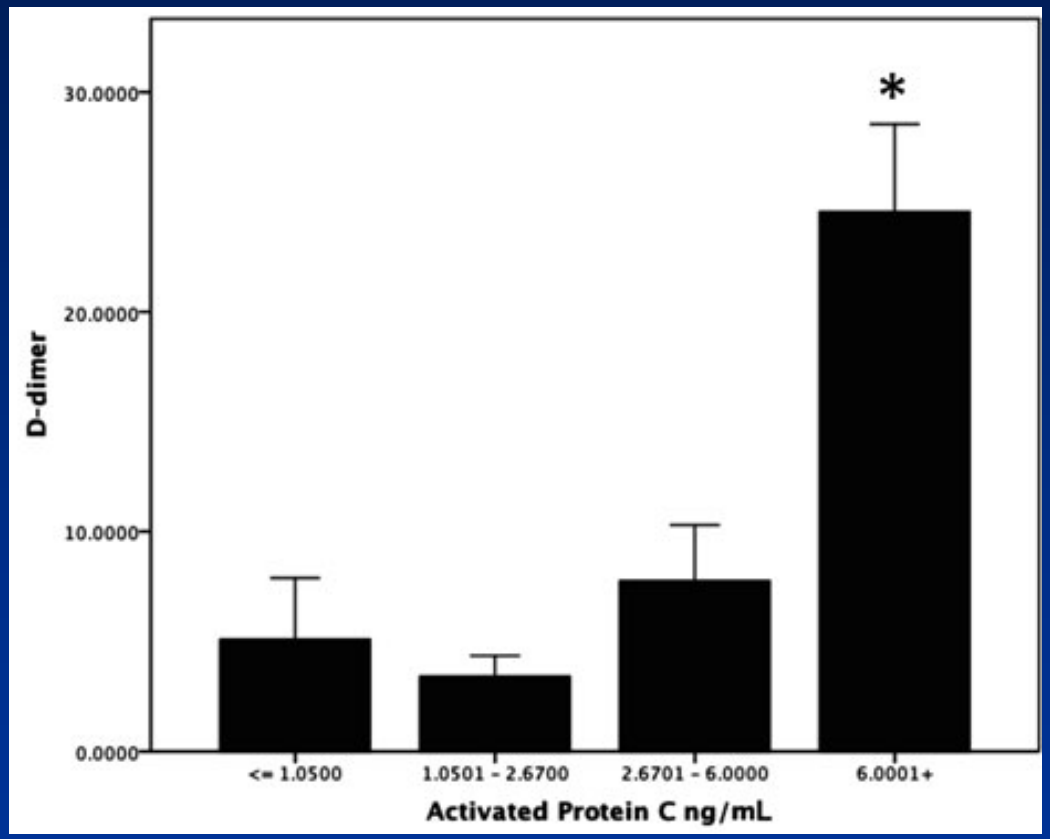

D-dimer levels in the 4 quartiles of activated PC

Coagulopatia e outcome clinici

I pazienti con trauma che arrivano in PS con la coagulopatia hanno 3-4 volte rischio di morte, in particolare nelle prime 24 h

La coagulopatia è un fattore predittivo indipendente per morte

L'aPTT predice meglio la mortalità rispetto al PT (OR aggiustato di 4.3 vs 1.4)

Livelli plasmatici alti di trombomodulina = OR di morte di 2.5

Livelli bassi di proteina C = OR di morte di 6.2

(Brohi J Trauma 2003; Macleod J Trauma 2003; Brohi Ann Surg 2007)

Ipercoagulabilità tardiva e rischio trombotico

Numerosi studi hanno dimostrato una ipercoagulabilità tardiva post-trauma

(Schreiber J Trauma 2005; Engelman World J Surg 1996; Boldt Crit Care Med 2000)

Il rischio di complicanze tromboemboliche è aumentato nei pazienti con trauma trauma (Knudson Ann Surg 2004)

È verosimile che una spiegazione consista nella precoce massiva attivazione della proteina C che conduce ad una deplezione di proteina C

Concezione attuale della coagulopatia acuta traumatica

Dopo trauma severo e ipoperfusione tessutale viene rilasciata (specie dall'endotelio) una grande quantità di sostanze antinfiammatorie e citoprotettive (tra cui trombomodulina e t-PA)

La Proteina C viene attivata in grande quantità dalla trombina circolante (formatasi per l'attivazione della coagulazione) unita alla trombomodulina

La aPC neutralizza FVIIIa e FVa, effetto anticoagulante con allungamento PT e aPTT

La aPC neutralizza PAI-1, che insieme al t-PA provoca iperfibrinolisi

Sopravviene poi la cosidetta coagulopatia iatrogena

La PC viene consumata e fortemente ridotta con aumento del rischio trombotico

Possible effects for future clinical intervention

(Cohen et al., Ann Surg 2012)

- Blocking of the anticoagulant domain of aPC early after trauma, which would correct the early posttraumatic coagulopathy, whereas maintaining the cytoprotective effect of that protein that is critical for the homeostasis of the vascular endothelium.
- Later, augmentation of the depleted PC response by the administration of a PC mutant that does not have the anticoagulant effect of the wild-type protein could be considered.