The Pathology and Clinical Problems of Chronic DIC

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The term consumption-coagulopathy (CC) describes the hemostatic defect encountered in clinical syndromes of dis-eminated intravascular coagulation (DIC). The basic event in CC and DIC is the intravascular activation of the coagulation system. This occurs as secondary complication in a number of diseases, which are known to involve the hemostatic system by one or more particular pathomechanisms.

Within my presentation I would like to summarize some clinical and diagnostic aspects of DIC, which have been of particular interest recently. I shall refer mainly to two clinical entities with regard to the acute and chronic development of DIC:

1. to shock, and
2. to cirrhosis of the liver

as models of acute and chronic hemostatic defects due to consumption-coagulopathy.

Slide 1
First of all CC requires a more specific definition:
it is characterized by three pathophysiological events:
1. procoagulant stimulation, which arises intravascularly and produces hypercoagulability,
2. concommittant deposition of microthrombi within the microcirculation and
3. defective hemostasis, due to an increased turn over to the hemostatic po-

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tential, particularly of fibrinogen, plasma factors and platelets.
This process may be self-limited if the compensating mechanisms active against intravascular coagulation are intact.

### Slide 2
These are:
1. the inhibitors of coagulation represented particularly by antithrombin III,
2. the activation of the fibrinolytic system, and
3. the clearance of activated endproducts of coagulation and fibrinolysis, such as thromboplastins, soluble fibrins and activators, by the RES. The RES function depends on the phagocytotic capacity as well as on the adequate perfusion of the RES. 50% of its total capacity is represented by the Kupffer-cells of the liver.

Failure of these compensating principles will consequently promote irreversible generalized microthrombosis. The important role of hemodynamic failure as contributing factor to the depression of RES capacity by decrease of circulatory clearance is evident.

The involvement of secondary fibrinolysis might be itself an indicator of DIC. It is caused by

### Slide 3
1. release of endothelial activator from vascular endothelium particularly from small veins,
2. the activator induces local lysis of microthrombi by local activation of co-precipitated plasminogen to plasmin,
3. following restitution of microcirculation fibrinolytic activators may invade systemic circulation promoting proteolytic degradation of circulating fibrinogen and further increased turn-over of the hemostatic potential. This attributes to severe hypocoagulability already induced by CC and may be followed at the endphase by the defibrination syndrome.

### Slide 4
Clinical manifestation of consumption-coagulopathy

<table>
<thead>
<tr>
<th>Bleeding tendency</th>
</tr>
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<tbody>
<tr>
<td>Evidence of impaired microcirculation</td>
</tr>
<tr>
<td>a) local: decreased organ function</td>
</tr>
<tr>
<td>b) systemic: shock</td>
</tr>
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With regard to the two decisive pathomechanisms operative in DIC-depletion
of the hemostatic potential and microthrombosis—the clinical manifestation of CC may be characterized by the evidence of a bleeding tendency and impairment of microcirculation, either locally or generalized, as encountered in shock.

Slide 5

As demonstrated by these figures published by REMMELE and HARMS microthrombosis is common autopic finding in patients who died from shock. It might be confirmed in up to 60% of the cases, where as the incidence of microthrombosis is only 8% in those cases who died from causes other than shock.

Microthrombotic events present themselves in different forms:

Slide 6 (spared)

such as occlusive microthrombi here in small vessels of the lung

Slide 7 (spared)

or eventually in form of globules, known as so called “shock bodies” which represent fibrin structures packed to globular particles.

Slide 8 (spared)

These may also show signs of degradation probably due to fibrinolysis. These fibrin globules are probably the morphological equivalent to soluble fibrin or fibrinmonomer-complexes, as defined biochemically.

Clinically, impairment of micocirculation associated with hemorrhagic phenomena present itself with picture of hemorrhagic necrosis particularly observed at the skin of the acra, as demonstrated by the following pictures of patients suffering from septic shock due to gram-negative bacteria.

Slide 9 (spared)

Skin lesions in the face

Slide 10 (spared)
at the fingers as gangreen, and

**Slide 11** (spared)
at the feet.

With regard to the fact that once DIC is involved, the prognosis of the clinical situation is doubtful, it is of utmost importance to establish. The diagnosis of CC as early as possible in order to care for preventive therapeutic measures. Therefore the analytical identification of CC is one of the most important tasks of the laboratory.

**Slide 12**
As far as the development of CC is concerned one may be confronted with all kinds of different results of coagulation studies, largely depending on the stage of DIC at the time of the first analysis. In general, three stages can be identified:

1. Hypercoagulability
2. Hypocoagulability either due to CC and secondary fibrinolysis, or
3. Defibrination, which renders the blood incoagulable.

The latter is observed rarely and may be eventually encountered as a complication in chronic DIC.

Although conventional assays may vary the degree of hemostatic decompensation, there is a great need for specific assays which allow the identification of the dominating of the dominating process responsible for the progressive degra-
dation of the hemostatic potential, either CC or fibrinolysis. Thanks to the advances in fibrinogen research methods are nowadays available which are suitable to make such differentiations.

Slide 13
As demonstrated by this graph indicating fibrinogen conversion, three enzymes —thrombin, fibrin stabilising factor and plasmin—compete for the same substrate, i.e. fibrinogen. Thrombin-induced fibrinogen-derivatives such as fibrinmonomer are representative for CC, whereas fibrinogen-and fibrin-degradation products as plasmin-induced derivatives are indicators of secondary fibrinolysis.

Slide 14 (spared)
Theoretically quantitation of soluble fibrin and FDP would allow to decide upon the dominating activation process, i.e. either CC or fibrinolysis. However, since fibrinmonomer is able to form high molecular weight complexes with FDP, it is difficult to assess both components separately. Quantitation of both components soluble fibrin and FDP, on the basis of fibrinogen equivalents are suitable to obtain at least comparative results. The identification of $\gamma$-$\gamma$-Dimer or Double D fragments is a definite indicator of sec. fibrinolysis and supplies retrospective evidence of previous CC.

Slide 15 (spared)
This chart represents a compilation of all assays available today which are suitable for the identification and qualification of thrombin-induced fibrinogen-derivatives. The assays for fibrinopeptide A and N-terminal glycine analysis are considered most specific, however difficult to perform. For clinical purpose quantitation of soluble fibrin and fibrinmonomer is achieved by means of either gel or affinity-chromatography, to which I would like to comment in the next slides.

Slide 16 (spared)
The simplest way to demonstrate qualitatively the presence of soluble fibrin in plasma is the ethanol gelation test. It is, however, false negative in presence of fibrinolysis and hypofibrinogenemia and false positive in hyperfibrinogenemia. Thus the interpretation of this test may be difficult.

Slide 17 (spared)
Gel filtration of plasma samples or plasma fractions according to FLETCHER as modified by GRAEFF separates high molecular weight fibrinogen derivatives from fibrinogen, as demonstrated by the shaded area, which can be quantita-
tively estimated by planimetry. The specificity of this procedure is proven by means of disc electrophoretic analysis.

Slide 18 (spared)

Furthermore fibrinmonomer may be selectively adsorbed from plasma on to insolubilized fibrinogen using fibrinogen-agarose columns for affinity-chromatography. Following desorption fibrinmonomer is accessible to quantitative determination. The principle of this method is based on the complex forming properties of fibrinmonomer with fibrinogen.

Slide 19

The next graph demonstrates the relationship of negative and positive ethanol tests to quantitative determination of fibrinmonomer by affinity-chromatography in patients with DIC. This graph showes that:

1. positive ethanol tests could be expected at fibrinmonomer levels above 7 mg/100 ml
2. negative ethanol tests do not exclude the presence of increased levels of fibrinmonomer.

The amount of fibrinmonomer usually correlated to the severity of CC involved in these cases.

Slide 20 (spared)

Quantitation of fibrinogen/fibrin degradation products (FDP) is achieved more
easily since quite a number of specific assays are available. They are compiled in this table. Most reliable are the Latex-agglutination and TRCHII assays. Within the next part of my presentation I would like to refer to the question: What is the diagnostic relevance of the fibrinogen derivative analysis? The question was whether the identification of fibrinogen-derivatives in clinical cases with DIC 1) is of value in prognostic evaluation of shock, and 2) indicates the cause of hemostatic defect with regard to the distinction between CC and fibrinolysis.

The results of a clinical study involving 94 patients with shock of different origins are summarized in the next two tables:

**Slide 21**
This graph demonstrates the mortality of patients with shock indicated by the lower parts of the column for the different forms of shock. The incidence of hemorrhagic complications due to defective hemostasis is shown by the black parts of the columns. In cardiogenic shock and septic shock, which had mortality rates up to 80%, hemorrhagic complication were negligible. In traumatic shock and other forms, however, hemorrhagic complications were more frequently observed in the groups of survivors.

**Slide 22**
The next slide shows the results of the analysis of fibrinogen derivatives as
determined by means of the described methods in the same patients, indicating fibrinmonomer in the upper and FDP in the lower part of the graph. There is a high incidence of positive FDP tests in the shock groups with high incidence of hemorrhage and high survival rate. On the other hand, high levels of fibrinmonomer are more frequently associated with shock forms revealing high mortality rates and inadequate fibrinolytic response.

In conclusion it can be confirmed that:
1. activation of secondary fibrinolysis following shock is an important determinant of prognosis,
2. hemorrhagic complications in shock must not necessarily be a sign of doubtful prognosis as its cause can be attributed to secondary fibrinolysis.

Slide 23
The factors operative in the interrelationship between shock and DIC are summarized in this graph. Shock and DIC may perpetuate themselves by CC and impairment of microcirculation. The involvement of hemorrhage seems more likely to be due to fibrinolysis than to CC. Bleeding, however, might, aggravate shock.

Slide 24
The essential pathogenetic factors operating as trigger mechanisms in shock are compiled in these tables. With regard to the different forms of shock they may not only help but also potentiate each other, particularly if one considers the role of the break-down of the compensating mechanisms such as potential fibrinolysis inhibitor and RES clearance in the manifestation of DIC in the
irreversible state.

In the last part of my presentation I would like to comment on some aspects of chronic DIC. The diagnosis of chronic CC possesses a number of problems, since this condition may not produce any clinical symptoms in its latent, so-called compensated state.

Slide 25 (spared)

One may suspect chronic CC if the following criteria are fulfilled:

1. the underlying disease may be considered as "conditioning" factor which predisposes the basis of its pathophysiology of the involvement of DIC and
2. if there is clinical evidences of unexplained recurrent episodes of thrombosis or signs of hemorrhagic diathesis or both,

This association of clinical signs may be observed in a number of diseases, particularly in metastatic carcinoma, vascular abnormalities and cirrhosis of the liver.

Slide 26 (spared)

The only exact method proving the involvement of DIC is the detection of an increased turnover of hemostatic components, which is achieved by means of platelet survival and fibrinogen half life studies. Labelled prothrombin and plasminogen may be used, too.

Slide 27 (spared)

Conventional coagulation studies are often unreliable since the hemostatic potential is kept constant due to adaption of synthesis of clotting factors of the increased turnover. This particularly is true in the case of fibrinogen. Its synthesis might be increased as a result of unspecific stimulation of protein synthesis. This often accounts for hyperfibrinogenemia in metastatic carcinoma and other malignancies.

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**Slide 28** Relation between fibrinmonomer- and fibrinogen-concentration in patients with DIC

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>n</th>
<th>FM mg/100ml</th>
<th>FG mg/100ml</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>shock and DIC</td>
<td>11</td>
<td>11.9±7.4</td>
<td>136±48</td>
<td>-0.83</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>meta carcinoma</td>
<td>19</td>
<td>4.5±2.2</td>
<td>521±208</td>
<td>0.91</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>liver cirrhosis</td>
<td>11</td>
<td>6.0±2.4</td>
<td>159±34</td>
<td>0.37</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>normal donors</td>
<td>27</td>
<td>1.97±0.36</td>
<td>279±80</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Slide 29** Hypofibrinogenemia in liver cirrhosis

**Pathomechanisms**

1. decreased protein synthesis
2. dysfibrinogenemia
3. dysproportional distribution of fibrinogen pool
   dilution
   extravasation
4. increased turn-over
Therefore the presence of hyperfibrinogenemia does not exclude the presence of DIC. Only by means of quantitation of fibrinmonomer one can decide whether DIC is involved or not. This table demonstrates the relationship between fibrinmonomer levels and fibrinogen concentration in three groups of representative conditions involving DIC:

1. shock and DIC
2. metastatic carcinoma, and
3. cirrhosis of the liver.

The correlation coefficients demonstrate that in acute CC there is a significant correlation between high levels of fibrinmonomer and hypofibrinogenemia. In metastatic carcinoma hyperfibrinogenemia correlates to high levels of fibrinmonomer, whereas in cirrhosis of the liver there is no relationship, although fibrinmonomer may be considerably increased. This indicates that in cirrhosis hypofibrinogenemia may also be caused by mechanisms other than consumption.

The decisive pathomechanisms contributing to hypofibrinogenemia in cirrhosis may be:

1. decreased synthesis
2. production of abnormal, easily degraded fibrinogen
3. disproportional distribution of fibrinogen pool due to dilution or extravasation into the “third space” i.e. ascites in presence of portal hypertension.

### Slide 30
In addition, there are further arguments against the involvement of DIC in cirrhosis which are based on the observation that:
1. the incidence of micorthrombi is low
2. anticoagulant therapy with heparin seldom does correct shortened platelet survival and fibrinogen half life
3. thrombocytopenia may be caused by sequestration of platelet in cases with splenomegaly.

### Slide 31
However, undoubtedly chronic CC must be at least partially involved, since it is a constant analytical finding. That thrombin—and plasmin—induced fibrinogen derivatives are increased, as demonstrated by this table including 18 patients with cirrhosis of the liver.

### Slide 32
The basic pathomechanisms responsible for the development of CC in hepatic disease include:
1. this release of procoagulant material from liver cell necrosis,
2. decrease of antithrombin and antiplasmin,
3. endothelial damage due to intestinal toxins,
4. impairment of RES clearance for coagulant and fibrinolytic activators, and
5. circulatory impairment due to portal hypertension.

### Slide 34 (spared)
Furthermore a decisive factor in maintaining chronic CC might also be the decrease of antithrombin III activity. This fact may also account for the failure
of heparin treatment in correction of shortened platelet survival and fibrinogen half life.

**Slide 35** (spared)

This possibility is demonstrated by this follow up study on a patient with cirrhosis of the liver, who showed no response to heparin therapy as indicated by normal thrombin times, despite of increasing heparin doses. However, following administration of a partified antithrombin III preparation, thrombin times were prolonged with increasing levels of antithrombin III in plasma. The efficiency of this treatment is confirmed by the fact, that fibrinmonomer levels were reduced following antithrombin III administration, as indicated on the boddom line.

**Slide 36** (spared)

What is now the present status of therapy of DIC? In conclusion, there is general agreement that the treatment of the underlying disease is the essential therapeutic approach in order to prevent DIC. In acute CC the challenger or trigger mechanism of procoagulant stimulation has to be eliminated. Heparin may be used either prophylactically or in therapeutic dosis if the increased turn over of hemostatic components has definately been verified by means of specific analytical procedures, and there are no contraindictions concerning hemorrhage. The hemostatic defect otherwise hat to bei treated by means of adequate substitution therapy with blood and plasma fractions. The use of natural inhibitors such as antithrombin III probably will be of advantage in the future.

**Slide 37**

Clinical experience has shown, that heparin is in effective in the following conditions associated with DIC: septicemia, septic shock, purpura fulminans, hemolytic uremic syndrome, hyaline membrane disease abruption placentae and graft refection.

**Slide 38**

In conclusion it has to be pointed put that all measures should be avoided, which, possibly may detoriate on or more of the compensating mechanisms. Irreversibility of DIC only can be prevented by the availability and functioning of inhibitor potential, secondary fibrinolysis and the clearance capacity of the RES in presence of adequate circulation and intact hemodynamic function within the microcirculation.