

POSITION  
OF THE DISSERTATION  
ROTARY THROMBELASTOMETRY AS A METHOD FOR EVALUATION  
OF HEMOSTASIC CHANGES AND RISK OF VARICOSE BLEEDING IN  
PATIENTS WITH LIVER CIRRHOSIS

for awarding the educational and scientific degree "Doctor"

on

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Pursuant to order № RD-26-1707 / 09.10.2020, the dissertation work and abstract of KAMEN VALENTINOV DANOV MD, Head of the Department of Gastroenterology at UMBALSM "Pirogov" was presented to me for a position.

The presented set of materials on paper and electronic media is in accordance with Articles 10 and 11 of the Law for the Development of the Academic Staff in the Republic of Bulgaria, Art. 32 of PPZRASRB for acquiring the educational and scientific degree "Doctor" and includes all necessary documents, prepared in accordance with the requirements.

The dissertation was discussed and proposed for defense on 09.09.2020. Discussed, adopted and directed for defense by a decision of the Scientific Council of 23.09.2020.

Liver cirrhosis is associated with complex defects in hemostasis, which to varying degrees involve the onset of the hemostasis cascade, coagulation and fibrinolysis. These defects are thought to be the cause of bleeding complications

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in patients with liver cirrhosis, and the unclear relationship between routine coagulation tests and the risk of bleeding is a problem in assessing behavior in these patients. The concept of a causal relationship between standard coagulation tests, such as PT, INR and aPTT, and the increased risk of bleeding is widely accepted among clinicians, but it is not confirmed in clinical practice or in attempts to assess complex hemostasis.

In patients with cirrhosis of the liver, changes in coagulation in the internal coagulation system are observed, which are not detected by routine tests. With regard to the external coagulation system, there are changes in coagulation that are not detected by routine tests, and the changes are significantly more pronounced in patients with an episode of bleeding from esophageal varices. It can be concluded that in patients with liver cirrhosis there are changes in coagulation that remain hidden from routine tests and these changes are significantly more severe in patients who have bleeding from esophageal varices. Quantification of known coagulation imbalance in liver cirrhosis is the key to establishing clinically useful information for determining the risk of bleeding in patients with liver cirrhosis. Various disorders have been observed in patients with a bleeding episode and those without a bleeding episode. In varicose bleeding, the presence of infection also causes coagulation abnormalities by generating endogenous heparinoids. Renal failure and endothelial dysfunction are other factors that contribute to hemostatic imbalance in cirrhotic liver. Another mechanism that is considered important in the pathogenesis of varicose veins in patients with liver cirrhosis is portal hypertension.

Further improvement of knowledge about the molecular mechanisms involved in the regulation of splanchnic and hepatic circulation leads to the emergence of new understandings based on evidence showing that not only the structural mechanisms but also the vasoactive components and elements of hemostasis have a significant importance for the complex pathophysiological mechanisms of the increased risk of varicose bleeding in some patients with liver cirrhosis. The current trend in the study of the risk of bleeding in patients with liver cirrhosis is evolving in the direction of searching for a reliable indicator or group of indicators that have significant predictive value and can be used to control therapeutic behavior. No scientific studies have been published on these issues in Bulgaria so far. Therefore, I believe that the dissertation of Kamen

Danov MD has a scientific-generalizing character and research-clinical orientation.

The introduction of K. Danov MD synthesizes the scientific scope of the dissertation and presents the problem that he will study in the dissertation, as well as its importance for the scientific field. In the literature review the dissertation presents the scientific achievements on the topic of the dissertation in the context of the goals and tasks set in the work. The main object of the dissertation of Danov MD hemostasis (primary and secondary) in norm and pathology and in particular in compensated and decompensated forms of cirrhosis is considered in detail in the context of the modern interpretation of the complex pathogenetic mechanism. Hemostasis is correctly presented as a factor that depends on the generation of thrombin (coagulation factors and platelets), fibrinogen substrate and clot stability. Danov MD demonstrates extensive knowledge of blood clotting processes, based on comprehensive information from published sources in this field. In the literature review, Danov MD also discusses issues that are debatable on the topic, which require further study and are a justification for the importance of the problem discussed in the dissertation. The cited literature sources are from recent years, and it is worth noting that very few Bulgarian authors have worked on the problem.

The aim of the dissertation is precisely and specifically formulated, derived from the literature review. There are five tasks and they are subordinated to the aim.

The study of Kamen Danov MD is prospective for patients hospitalized in the University Hospital "N. I. Pirogov "and UMHAT" Alexandrovska "for the period 2013-2020. 108 patients were examined. The first group included patients who were hospitalized for bleeding from esophageal varices or patients hospitalized for cirrhosis of the liver who had an episode of bleeding from esophageal varices. The second group included patients who were hospitalized for treatment of liver cirrhosis, had no history of bleeding from esophageal varices, and no bleeding was detected on endoscopic examination. The third group included patients without liver pathology, without evidence of esophageal varices and without evidence of bleeding of any origin.

Hemostasis was examined in all patients by determining prothrombin time in seconds and percentage, aPTT and INR. All patients underwent rotational thrombelastometry on an automatic ROTEM Sigma analyzer.

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Studies were performed in the following four panels: EXTEM recombinant tissue factor and phospholipids to activate the external system and the general coagulation pathway; INTEM partial thromboplastin from rabbit brain kaolinase activation of the internal system and the common coagulation pathway; FIBTEM recombinant tissue factor, phospholipids and cytochalazine D to inhibit platelet function; HEPTTEM rabbit brain partial thromboplastin kaolin and heparinase for heparin degradation.

The results of the study by K. Danov MD show the importance of changes in hemostasis as an important factor for varicose bleeding along with traditional understandings of the importance of portal hypertension. The establishment of hypercoagulable disorders does not contradict the understanding of the sinusoidal component of portal hypertension. Various studies have shown that the sinusoidal component accounts for 30% to 40% of increased intrahepatic resistance. The hypothesis of multiple microthrombosis or a condition of "consumptive coagulopathy" that affects the sinusoids is fully confirmed in the study of the dissertation.

Danov's study found that patients with cirrhosis of the liver had normal INR values with slight changes in rotational thrombelastometry. INR values do not have a clear correlation with the presence of bleeding in patients with esophageal varices. There is no correlation between INR and the values in EXTEM, which accurately indicate the state of the external coagulation system. To an even lesser extent, there is an association between aPTT values and INTEM values. Patients with a bleeding episode had aPTT values that were closer to normal compared to patients with cirrhosis without a bleeding episode. If severe coagulation disorders and an increased risk of bleeding from esophageal varices can be suspected at extremely high INR values, such dependence is not established with aPTT. Platelet count is a parameter that shows an association with the presence of bleeding in patients with liver cirrhosis. Patients in group I had lower platelet counts than group II.

In the discussion of the results of K. Danov's research, an analysis of his results in the context of the literature data was performed. The dissertation also shows the contributing moments of his dissertation.

According to the dissertation, the study of hemostasis in liver patients has many aspects and its study, in addition to clarifying certain issues of liver pathology, provides guidelines for even more in-depth research in this area. Rotational

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thrombelastometry is a method that has proven its effectiveness in monitoring coagulation changes in patients with cardiovascular pathology, perioperative complications, congenital hemostasis deficits and traumatic coagulopathies. His research shows that the method has applicability in the assessment of liver pathology, which is known to be accompanied by numerous changes in blood clotting and normal hemostasis function.

The studied material is sufficient in volume and allows reliable statistical processing with reliable results. The selection of patients and the examinations were carried out according to the generally accepted standard methods.

The dissertation is written on 197 standard pages, of which 1 page-title, 1 page-content, 2 pages-used abbreviations, 4 pages-introduction, 49 pages-literature review, 1 page-aim and objectives, 6 pages-materials, 3 pages - methods, 94 pages - results, 5 pages - discussion, 1 page - conclusion, 2 pages - inferences, 1 page - contributions, 27 pages - bibliography, 1 page - publications.

The dissertation work of K. Danov MD is well arranged and illustrated, it is very easy to read. It is stylistically sound and free of spelling mistakes.

K. Danov MD has presented 4 scientific publications in connection with the dissertation, and in these publications he is a leading author.

After getting acquainted in detail with the scientific work of Kamen Danov MD, I believe that the work is dissertable, innovative and will use gastroenterologists from the country in their daily work. The author has indisputable qualities, proven in the long and successful clinical practice in leading medical institutions. The dissertation meets the requirements, which is why I allow myself to recommend to the respected members of the scientific jury to vote positively and to award Kamen Danov MD the educational and scientific degree "Doctor".

10/12/2020

Prof. Iliya Petrov Lozev, MD, PhD, DSc