
REVIEW

From Prof. Nikola Grigorov, MD, PhD, DCs

On the dissertation work of Kamen Danov MD from the Department of Gastroenterology at the University Hospital "N.I. Pirogov" on "Rotational thrombelastometry as a method for assessment of hemostasis changes and risk of varicose bleeding in patients with liver cirrhosis" for obtaining the educational and scientific degree "Doctor" in the field of Higher Education 7; Health and sports; professional field 7.1 Medicine; scientific specialty Internal medicine.

The procedure is followed according to the Regulations for application of the law for the development of the academic staff in the Republic of Bulgaria. The doctoral student presents its own scientific and scientific-practical results in the field of clinical medicine, which has proved in-depth theoretical knowledge and practical skills during his work in the Department of Gastroenterology of UMHATEM "NI Pirogov".

The introduction defines the scientific scope and more extensively than usual sets out the problem to be solved in the dissertation. Hemostasis and routine tests for its diagnosis in compensated and decompensated liver cirrhosis are presented through generally accepted concepts with cited authors (unusual in this part of the dissertation). The blood clotting scheme and some of the judgments would be better in the literature review.

The review begins with a modern interpretation of portal hypertension, which is considered to be the main, according to some, the only factor for varicose bleeding in an abnormal portal gradient. The relationship between sinusoidal endothelial cells and the stellate response that initiates and maintains fibrogenesis, intrahepatic circulation (complex acquired mechanism), liver-kidney axis, new suggestions for increased thrombosis in the course of the

disease, loss of fenestration at the cellular level and of hepatocytes, change in the molecular phenotypes of sinusoids, initiation of neoangiogenesis at the sinusoid level and other phenomena at the cellular and ultracellular level. Proven pathogenetic mechanisms have changed perceptions of the cirrhosis process and provided hope for upgrading the treatment strategy with vasoactive drugs that relieve peripheral vascular, sinusoidal resistance. Discussing the circulatory nuances of cirrhosis in a state of peripheral resistance and splanchnic dilatation (role of NO), Danov MD emphasizes the two main theories (back and forward flow), which are two sides of the same coin, not a preferred fact. Moses Folkman sees the collateral network as an angiogenetic process, which, however, is a consequence of altered cell interactions and signaling pathways. The pathogenesis of portal hypertension is not fully deciphered about the role of the arterial and portal system in utilization, the importance of the so-called "first pass" of metabolites, adrenergic vasomotor regulation, cardiac volume, sensory neurons, dilator peptide volume and others. unexplored mechanisms. It is certain that the portal flow is controlled by splanchnic arterioles and less by vascular intrahepatic structures. This part of the review is an in-depth, comprehensive profile of the main cirrhosis syndrome and a working basis in the dissertation.

The main object of the dissertation - hemostasis (primary and secondary) in norm and pathology and in particular in compensated and decompensated forms of cirrhosis is considered in details, 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. He does not make a bibliographic list of author's materials and theoretical discussions, but focuses on authoritative works that challenge and change existing concepts. The processes of primary and secondary hemostasis are discussed in a critical context in compensated and decompensated cirrhosis: quantitative and qualitative changes in platelets (myelosuppression, impaired thrombopoietin synthesis, segmentation, increased destruction, but also intravascular disseminated cell coagulation) regulatory control. Thrombocytopenia may be due to cell depletion with preserved production, which to some extent contradicts the generally accepted ultimate role of hypersplenic thrombocytopenia.

The mechanism of secondary hemostasis in cirrhosis with changes in the pro- and anticoagulant level is another discussed phenomenon in which an unexpected abnormality is observed in the latter. The process is complicated and suggests another pattern of platelet involvement in advanced cirrhosis.

Following is a presentation of the standard tests for coagulation and their place in the detection and staging of liver diseases - their diagnostic, including prognostic value and shortcomings. The so-called viscoelastic coagulation tests, measuring the whole process - from the start of fiber formation to the final product, as well as alternative coagulation methods.

Thrombelastometry, as a method for assessing the elastic properties of the clot, providing real-time information on quality and kinetics, is presented in detail - from the basic principles (schemes and figures), derivation of parameters, diagnostic advantages, capabilities and limitations, to standardization of methodology.

The following is the correlation of the conventional coagulation tests with the used viscoelastic parameters with respect to fibrinogen, the current functional platelet stability, fibrinolysis. Pathogenetic mechanisms already discussed are repeated in places.

Bleeding from varicose veins of the esophagus, stomach and portal gastropathy are major complications of portal hypertension with a mortality rate. The syndrome depends directly and indirectly on drug and endoscopic prevention. The risk is primarily related to increased portal basin pressure - above 12 mmHg, correlated with increased 7 - 10 mmHg portosystemic gradient (HVPG), splanchnic vasodilation, decreased v.azygos pressure, conditionally accepted and unaccepted bacterial translocation by GIT . Prevention is carried out by non-selective β -blockade, combination with α -blockers to achieve splanchnic vasoconstriction (in varicose veins over 5 mm.), Endoscopic ligation and sclerotherapy (no significant difference) and follow-up every 1 year, as the portal pressure increases ultimately by about 20-25% in 1.5 - 2 years in the course of cirrhosis. This information is important and is related to the topic of the dissertation, more precisely to the enrichment of the panel for the prevention of the risk of bleeding.

The review ends with practical skills in working with the equipment.

Danov MD's literary review is comprehensive, with in-depth knowledge of the complex material that underlies the dissertation. It points out disagreements, raises questions that do not have an unambiguous answer and requires further research. It serves as a justification for the value of the dissertation and more precisely what are the expectations for its scientific and scientific-practical contribution.

The aim of the dissertation is precisely formulated. It is based on a modern, more precisely updated method of rotational thrombelastometry to assess hemostasis and in particular the risk of varicose bleeding in cirrhosis.

The tasks are related to the evaluation of the diagnostic parameters of the method from their value as independent criteria to their inclusion in a diagnostic algorithm.

The clinical study used a large number of patients (108) with strictly defined inclusion and exclusion criteria regarding the disease process (cirrhosis) and graphically represented groups with and without episodes of bleeding, hemoglobin level, comorbidity, control.

Rotational thrombelastometry in four panels, performed in all patients, gives the following indicators: clotting time, clot formation time, maximum clot strength (resistance), thrombodynamic potential.

A respectful package was used to process the results, which includes 10 statistical methods.

The results begin with the data of the three groups (cirrhosis without, with bleeding and control) of the conventional hemostasis tests, platelet count (topicality), CRP, Leucocytes (inflammation), and continue with a perfect presentation through multiple graphs of the parameters CT and CFT, A10, 20, 30, MCF, TPI, etc. of the metric tests INTEM, EXTEM, FIBTEM, HEPTM. The dynamics emphasize some more important metric indicators that determine self-diagnosis.

This part of the dissertation fully corresponds to a completed scientific work.

Discussion of the results is open to the problems posed by liver cirrhosis in terms of hemostasis, through defects affecting coagulation and fibrinolysis. Routine tests are unsatisfactory to determine the risk of complications - bleeding. Danov MD sets the rotational elastometry through its derived

parameters as a reliable superstructure method, which accurately informs about the coagulation respectively the risk of bleeding. His arguments are convincing and are based on a perfectly conducted clinical study. It allows to include the disturbed hemostasis in the pathogenesis of varicose bleeding, which contradicts the absolute role of portal pressure. Danov MD confirms the concept of the so-called microthrombotic sinusoidal "consumptive coagulopathy". Whether this is the relationship with platelet count, which should be discussed in a complex context, remains to be seen.

As a component of hemostasis, fibrinolysis, with all its complexity from the balance of inhibitors and activators, changes in cirrhotic patients. It is activated, which makes the clot unstable. However, in a small group of patients with liver cirrhosis, its reduced activity is observed as a result of complex etiopathogenetic components that are present at all stages of hemostasis. This makes routine testing problematic, in contrast to the greater possibilities of thrombelastometry.

The additionally calculated thrombodynamic potential index (TDI), using all parameters of the tests to assess the internal and external coagulation system, is able to predict the risk of bleeding, showing a significant difference in stationary cirrhosis and varicose veins, ie. shows the general tendency of hemostasis in the course of cirrhosis. This part of the dissertation closes the circle of elastometry contributions in the course of the cirrhotic process from a theoretical (participation of hemostasis in its entire volume, not details of it) and practical (bleeding prevention) point of view.

The conclusion is well formulated. It corresponds to the results of the clinical trial and their discussion in the previous chapter.

The inferences are adequate, with a specific focus, without exceeding the threshold of competence achieved by the conducted clinical trial. They should be more specific, not unnecessarily descriptive.

The literature includes 254 well-selected articles and authors, with lower Bulgarian participation (view of the dissertation), except for those related to statistical processing. With a few exceptions, they are spelled correctly, in alphabetical order, rather than the preferred numbering according to the text of the dissertation.

Kamen Danov MD is a build specialist in Gastroenterology, consultant and expert. After a successful university career, he approved the organization and

staff of the newly established Department of Gastroenterology at UMHATEM "Pirogov" as its first head. His clinical activity includes routine and advanced methods for diagnosis and treatment of a number of diseases, primarily in the field of gastroenterology (upper and lower endoscopy) and hepatology (abdominal ultrasound). He has an enviable awareness, which defines him as a fully developed professional with a scientific focus. Entering the unusual field of practical innovative medical science, Danov MD accepted the challenge of a researcher and successfully defended it.

The dissertation of Kamen Danov MD is a quality product of a motivated doctor with a serious knowledge capacity. It presents in full an updated, almost unknown to gastroenterologists and internists diagnostic method in the rarely discussed, problematic and incompletely understood area of hemostasis in liver pathology.

The self-assessment of the dissertation through the conclusions is correct, but in my opinion it is insufficient. Danov MD enters into a discussion and manages to convince theoretically the participation of hemostatic changes in the complex pathogenesis of portal hypertension and more precisely its life-threatening complications. He accepted that in parallel with the complex hemodynamic changes in cirrhosis, there was a critical reorganization / abnormality of the whole hemostasis process, initially discrete, later demonstrative, whose information gives him a detailed analysis of elastometry, unconvincing conventional tests.

The introduction of elastometry in everyday practice without preparation and interpretation of data is unlikely to change the diagnostic and treatment algorithm. Its use in the context of the clinic, staging and monitoring of cirrhosis in its natural course, as a chronically progressive disease, will enrich the knowledge and especially the prevention of critical complications. Therefore, additional observations and critical discussions of patients with different etiological forms of cirrhosis, at different stages of the disease are forthcoming. New methods with promising claims are entering clinical practice, but the clinic is a judge of their effectiveness. That is why at this stage Danov MD is a pioneer of a promising methodology, which was generally expected by specialists.

Therefore, the dissertation has certain contributions of theoretical, scientific and scientific-practical significance. It includes a high level of theoretical knowledge on the problem, perfectly performed research with nuances of innovation and

professional analysis of the results, which predetermines the routine use in clinical conditions of rotational thrombelastometry.

The dissertation of Kamen Danov MD "Rotational thrombelastometry as a method for assessing hemostasis changes and the risk of varicose bleeding in patients with liver cirrhosis" fully meets the requirements for awarding the educational and scientific degree "Doctor".

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Signature:

Prof. N. Grigorov