Medicine®

Rotational thromboelastometry in patients with type 2 diabetes and mild COVID-19 pneumonia

A pilot prospective study

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Abstract

Background: It was repeatedly demonstrated that patients with severe COVID-19 pneumonia, as well as patients with type 2 diabetes (T2D) have higher risk of thromboembolic complications. Rotational thromboelastometry (ROTEM®) is a viscoelastic hemostatic assay which allows complex assessment of hemostasis in whole blood. The aim of this study was to compare changes in hemostasis measured by ROTEM® in diabetic and nondiabetic patients with mild COVID-19 pneumonia.

Methods: We performed a pilot, prospective, observational study and enrolled 33 consecutive patients (14 with T2D and 19 nondiabetic ones) admitted to regular ward with mild COVID-19 pneumonia. The control group consisted from 11 healthy, nondiabetic blood donors. Blood samples were tested with ROTEM® using INTEM® and EXTEM® reagents.

Results: We detected significant differences in EXTEM® clotting time (CT), clot formation time (CFT), and maximum clot firmness (MCF) comparing patients with mild COVID-19 pneumonia and healthy donors. However, there were no significant differences in EXTEM®, INTEM®, and HEPTEM® parameters (CT, CFT, and MCF) according to diabetes status.

Conclusions: Our study demonstrated hypercoagulation in patients with mild COVID-19 pneumonia. T2D did not affected ROTEM® parameters in patients with mild COVID-19 pneumonia.

Abbreviations: CFT = clot forming time, COVID-19 = coronavirus 2019 disease, CT = clotting time, DCCT = Diabetes Complications and Control Trial, ICU = intensive care unit, MCF = maximum clot firmness, PAI-1 = plasminogen activator inhibitor-1, PCR = polymerase chain reaction, ROTEM = rotational thromboelastometry, SARS-CoV-2 = severe acquired respiratory syndrome-coronavirus-2, T2D = type 2 diabetes mellitus, VHA = viscoelastic hemostatic assay, VTE = venous thromboembolism.

Keywords: mild COVID-19 pneumonia; rotational thromboelastometry; ROTEM®; type 2 diabetes

1. Introduction

Patients with confirmed coronavirus SARS-CoV-2 (COVID-19) pneumonia have high risk of thromboembolic complications, and patients presenting with these complications have higher risk of death.[1,2] This higher risk of thrombosis, described mostly in patients with severe COVID-19 pneumonia, is connected with hypercoagulation and fibrinolysis shutdown.[3,4] Rotational thromboelastometry (ROTEM®) is a viscoelastic hemostatic assay (VHA) which allows complex assessment of several hemostatic components in whole blood

sample, and which might overcome some disadvantages of traditional laboratory tests.[5] In a previous study, Mitrovic et al showed that hypercoagulable ROTEM® pattern characterized by clot formation acceleration, high clot strength, and reduced fibrinolysis was more frequent in severe COVID-19 pneumonia.[6]

ROTEM® (Instrumentation Laboratory, Bedford, MA) is a point of care VHA which assesses (in real time) clot formation/dissolution and strength by measuring the amount of a continuously applied rotational force that is transmitted to an electromechanical transduction system by the developing clot. The test

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is based on a solid, constantly oscillating pin in a fixed cup with a whole blood sample with reagents. As the strength of the clot increases, the rotation in the system is obstructed and graphically recorded in the form of a thromboelastogram. ROTEM® testing can be performed with a variety of activators and inhibitors, which are commercially available as ROTEM® assays/ tests. The INTEM® test is initiated by activating the intrinsic pathway; EXTEM® test is initiated by activating the extrinsic pathway; FIBTEM® corresponds to an EXTEM® with the inhibition of platelets, and HEPTEM® corresponds to an INTEM® with the addition of heparinase, which degrades heparin and allows the analysis of heparinized samples. Several parameters can be measured during ROTEM® analysis; the most important ones are: clotting time (CT) – represents the time elapsed from the coagulation trigger until the formation of a clot of 2 mm; clot forming time (CFT) – represents the time elapsed from 2 to 20 mm; and maximum clot firmness (MCF) – represents the maximum clot strength. ROTEM® is mostly established in the management of bleeding during trauma or surgery (hepatic or cardiac); however, it might also be used during the treatment of several cardiovascular diseases. As mentioned, the assay has the ability to overcome some disadvantages of traditional hemostatic tests, such as longer turnaround times, lack of sensitivity to some abnormalities in clot formation, the inability to diagnose complex coagulation disorders, the inability to assess coagulation under hypothermic conditions, and the low predictability of bleeding resulting from invasive procedures. However, ROTEM® may have several limitations. Clot formation and lysis is connected with a wide range of normal values (as there is a high variability of the components of the hemostasis) and there is an issue with assay standardization (as the technique diversifies in terms of modifications, equipment and activators). ROTEM® might be performed with a variety of reagents (activators and inhibitors), which alerts the specificity of the assay (this has been, in part, overcome with commercially available ROTEM® reagents). Moreover, the changes of ROTEM® parameters are not specific. For example, clotting time could be prolonged due to inherited coagulation disorder, or acquired coagulation disorder (such as liver failure), or drug-induced (due to anticoagulation), thus knowing the patient history or additional laboratory testing might be needed for appropriate interpretation of ROTEM® results.[5,7]

Type 2 diabetes mellitus (T2D) is connected with hypercoagulation and is a known risk factor for venous thromboembolism (VTE). A previous meta-analysis reported a 1.4-fold increased risk of VTE in patients with T2D.[8] In addition, Feuring et al demonstrated increased coagulability in patients with T2D compared to nondiabetic patients in a ROTEM® analysis.[9] Thus, it seems that risk of hypercoagulation could be in patients with mild COVID-19 pneumonia increased with the presence of T2D. As there is no study specifically testing the effect of T2D on ROTEM® parameters in patients with mild COVID-19 pneumonia, we decided to perform one. The aim of this study was to compare changes in hemostasis measured with ROTEM® in diabetic and nondiabetic patients with mild COVID-19 pneumonia.

2. Patients and Methods

2.1. Study design, sample selection, blood sampling, and laboratory testing

This was a pilot, prospective, observational study. The study enrolled prospectively consecutive patients who required in-hospital admission for mild COVID- 19 pneumonia. A confirmed SARS-CoV-2 infection by PCR test, mild clinical symptoms, and chest X-ray or computer tomography changes corresponding with COVID-19 pneumonia were required for patient enrollment in COVID-19 mild pneumonia group. Patients with known

T2D were enrolled to T2D subgroup. In patients with no history of diabetes a screening for unknown T2D was performed prior enrollment of a patient to nondiabetic subgroup. This screening was based on glycated hemoglobin examined at admission and standard oral glucose tolerance test (75 g of glucose was mixed with 250 ml of water, swallowed orally and blood samples were taken 1 and 2 hours after ingestion) performed 1 month after patient discharge (as acute COVID-19 pneumonia could affect the results). Only individuals with glycated hemoglobin levels < 5.7% DCCT (Diabetes Complications and Control Trial) and blood glucose level at 2nd hour of oral glucose tolerance test < 7.8 mmol/L (140 mg/dL) were enrolled in nondiabetic group for final evaluation. Patients were excluded if they had signs and symptoms consistent with severe COVID-19 pneumonia, had chronic anticoagulation, known inherited/acquired bleeding disorder, severe kidney disease (stage 3B – 5 of chronic kidney disease or stage B-C of acute kidney injury), and severe liver disease (defined as liver cirrhosis Child B-C or acute liver injury with hepatic encephalopathy and/or severe loss of liver function). Chronic antiplatelet therapy was not a contraindication for patient enrollment. All patients received subcutaneous low molecular weight heparin prophylaxis with enoxaparin dosed 30 mg subcutaneously once daily during their in-hospital stay. No other antithrombotic drugs were given in patients with mild COVID-19 pneumonia. Data from healthy sex-matched blood donors from preCOVID-19 era who agreed to participate in our ROTEM® clinical research[10] were analyzed as controls. PCR test for SARS-CoV-2 was not performed in these control individuals because the ROTEM® testing was performed in preCOVID-19 era (February 2019). No antithrombotic therapy was administrated in control healthy blood donors. All the controls underwent oral glucose tolerance testing, and only those with blood glucose level at 2nd hour of the test < 7.8 mmol/L were enrolled for final evaluation. The research was formally approved by our institutional ethical review board (Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava). All individuals agreed to participate in the study, and signed written informed consent for study participation and blood sampling (specific written informed consent for this study was also obtained in control blood donors who were sampled for our previous study[10]).

Blood samples were taken on the third day of in-hospital stay, blood samples were collected to sodium citrate-containing vacutainer plastic blood collection tubes at 7:00 AM, and these samples were tested with ROTEM®[5] within the hour after blood sampling. ROTEM® testing[10] was performed on ROTEM® Gamma (Pentapharm GmbH, Munich, Germany) analyzer with INTEM®, EXTEM® and HEPTEM® reagents in patients with COVID-19 pneumonia and with INTEM® and EXTEM® reagents in controls (as no heparin therapy was administrated in controls) according to instructions from the manufacturer. We measured the following variables: clotting time (CT), clot forming time (CFT), and maximum clot firmness (MCF).

2.2. Statistical analysis

Data analysis was performed using STATISTICA v 5.0 (StatSoft, Tula, USA). Data were checked for normality with the Shapiro–Wilk test (data are reported as mean ± standard deviation in case of normal distribution and as median and interquartile range in case of asymmetrical distribution); a t-test was used in the case of normally distributed data or a Mann–Whitney U test was used when data distribution was asymmetrical. The P-value of <0.05 was considered as a statistically significant difference.

3. Results

During the study period 33 consecutive patients (14 with known T2D type 2 diabetes and 19 nondiabetic patients fulfilling study

Table 1

Basic demographics and therapy in patients with mild COVID-19 pneumonia (with and without type 2 diabetes) and in healthy donors.

	Mild COVID-19 pneumonia patients with DM	Mild COVID-19 pneumonia patients without DM	Healthy donors
Number of patients	14	19	11
(men/women)	(7/7)	(6/13)	(5/6)
Age	79 (65–94)	71 (31–94)	56 (31–63)
Beta-blockers (%)	64.2	52.6	0
Diuretics (%)	21.4	10,5	0
Digoxin (%)	7.1	5.2	0
ACE inhibitors, AT1RB (%)	42.8/0	31.5/10.5	0
Aspirin (%)	21.4	15.7	0
BMI (kg/m²)	31.9	33.1	24.5
Serum creatinine (umol/L)	124.4 ± 53.7	79,1 ± 40.3	73.3 ± 15.3
Calculated GFR–Cocroft Gault (ml/min/1.73 m²)	54.2	89.1	90.0
Total bilirubin, (mmol/L)	9.5 ± 4.1	9.6 ± 4.3	7.6 ± 3.1
Total Serum Protein, (g/L)	62.5 ± 7.9	60.2 ± 7.4	64.1 ± 9.4
Platelet counts (10⁹/L)	299 ± 83.7	265.4 ± 140.5	289 ± 50.8
Hemoglobin (g/L)	119.6 ± 12.1	117.2 ± 17.4	123.5 ± 14.8
INR	1.16 ± 0.13	1.13 ± 0.14	1.08 ± 0.12
APTTr	0.89 ± 0.22	1.03 ± 0.17	0.97 ± 0.19
TT (sec)	14.7 ± 1.9	14.2 ± 2.1	13.9 ± 1.5
D-dimer (mg/L)	4.9 ± 6.7	2.5 ± 3.3	Not estimated
Fasting glucose level (mmol/L)	9.7 ± 3.9	5.8 ± 0.9	4.3 ± 0.3
Glycated hemoglobin (% DCCT)	6.7 ± 1.4	4.9 ± 0.3	Not estimated
Diet only (%)	21.4	N/A	N/A
Oral antidiabetic drugs (%)	21.4	N/A	N/A
Insulin therapy without oral drugs (%)	28.6	N/A	N/A
Insulin therapy with oral drugs (%)	28.6	N/A	N/A
Hypoxia (%)	57.1	45.8	N/A
C-reactive protein (mg/L)	72.0 ± 44.2	72.4 ± 44.9	Not estimated
Antipyretics (%)	57.1	50.0	N/A
Antibiotics (%)	50.0	47.4	N/A
Corticosteroids (%)	92.8	100	N/A
Antiviral drugs (%)	14.3	8.3	N/A
Vitamins (%)	100.0	100.0	N/A

ACE = angiotensin converting enzyme, APTTr = Activated Partial Thromboplastin Time Ratio, AT1R = AT1 receptor, BMI = body mass index, DCCT = Diabetes Complications and Control Trial, GFR = glomerular filtration rate, INR - International Normalized Ratio, N/A = not appropriate, TT = thrombin time.

inclusion criteria) who required in-hospital admission for mild COVID-19 pneumonia were enrolled. The average age was 69 years (31–89 years); the mild COVID-19 pneumonia group consisted from 13 men and 20 women. Three patients in both subgroups (i.e., 3 patients with T2D and 3 patients without T2D) had chronic aspirin therapy. Additionally, ROTEM® data from 11 sex-matched healthy blood donors from preCOVID-19 era were analyzed as a control group. The basic demographic data and chronic medication in patients are stated in Table 1.

There were no significant differences among patients with mild COVID-19 pneumonia according to T2D status in basic demographic data and in concomitant therapy (Table 1).

In the first step of ROTEM® analysis (Table 2), patients with mild COVID-19 pneumonia were compared with healthy controls. This comparison showed significant differences in EXTEM-CT, CFT, and MCF between patients and healthy controls. In addition, significantly longer INTEM-CT was found in COVID-19 pneumonia patients compared to controls (227.1 ± 104.9 vs 163.8 ± 5.8 seconds., $P \leq 0.001$), but no significant differences were found in INTEM-CFT (72.4 ± 37.7 vs 84.3 ± 4.3 seconds., $P=0.43$) and in INTEM-MCF (67.5 ± 7.2 vs 67.9 ± 8.5 mm, $P=0.28$).

In the second step of ROTEM® analysis (Table 3), ROTEM® data were compared in patients with mild COVID-19 pneumonia according to T2D status. For EXTEM-CT, there were no statistically significant differences comparing patients with T2D and nondiabetic patients (72.1 ± 7.9 vs 72.8 ± 14.1 seconds, $P=0.87$). Similarly, there were no significant differences in EXTEM-CFT and EXTEM-MCF between patients with

T2D and those without diabetes (EXTEM-CFT: 63.7 ± 21.7 vs 59.1 ± 17.1 second., $P = .55$; EXTEM-MCF: 69.9 ± 6.4 vs 70.8 ± 5.6 mm, $P = .68$). In addition, no significant differences were found in INTEM-CT, INTEM-CFT, and INTEM-MCF between diabetic and nondiabetic patients with mild COVID-19 pneumonia. Finally, HEPTEM parameters (HEPTEM-CT, HEPTEM-CFT and HEPTEM-MCF) did not differ significantly in COVID-19 pneumonia patients according to their T2D status.

4. Discussion

Several studies and a meta-analysis demonstrated that patients with severe COVID-19 pneumonia are at high risk of thromboembolic complications.[11,12] It seems that higher risk of thrombosis is due to COVID-19-related hypercoagulation, as Mitrovic et al demonstrated, by elevated values of ROTEM® parameters (EXTEM-MCF and FIBTEM-MCF), that patients with COVID-19 had hypercoagulable ROTEM® pattern already on admission.[6] In addition, Spieza et al[13] previously reported severe COVID-19-related hypercoagulation in patients admitted to intensive care units (ICU) for acute respiratory failure due to COVID-19 pneumonia. In this study, ROTEM® profiles of these patients showed shorter CFT in INTEM® and EXTEM® and higher MCF in INTEM®, EXTEM® and FIBTEM®. Another descriptive study examining 29 COVID-19 patients showed a significantly increased clot lysis resistance and significantly higher plasminogen activator inhibitor-1 (PAI-1) activity, which correlated with increased clot lysis time, in ICU COVID-19 patients.[14] The observation of COVID-19-related

Table 2

ROTEM® analysis in patients with mild-COVID pneumonia vs healthy donors.

	Mild COVID-19 pneumonia	Healthy donors	*P*-value
EXTEM-CT (sec)	72.6 ± 12.5	55.2 ± 6.5	*P* < 0.0001
EXTEM-CFT (sec)	60.5 ± 18.8	80.0 ± 23.8	*P* < 0.05
EXTEM-MCF (mm)	70.5 ± 5.9	63.5 ± 4.2	*P* < 0.0001
INTEM-CT (sec)	227.1 ± 104.9	163.8 ± 5.8	*P* < 0.001
INTEM-CFT (sec)	72.4 ± 37.7	84.3 ± 4.3	*P* = .43
INTEM-MCF (mm)	67.5 ± 7.2	67.9 ± 8.5	*P* = .22

p = significance, clotting time (CT), clotting forming time (CFT), and maximum clot firmness (MCF), sec. = seconds, mm = millimeter.

Table 3

ROTEM® analysis in mild COVID-19 pneumonia: T2D vs no diabetes.

	T2D	No diabetes	*P*-value
EXTEM-CT (sec)	72.1 ± 7.9	72.8 ± 14.1	*P* = .21
EXTEM-CFT (sec)	63.7 ± 21.7	59.1 ± 17.1	*P* = .55
EXTEM-MCF (mm)	69.9 ± 6.4	70.8 ± 5.6	*P* = 0.68
INTEM-CT (sec)	217.3 ± 104.1	231.7 ± 104.1	*P* = .72
INTEM-CFT (sec)	87.1 ± 53.3	66.3 ± 8.2	*P* = .24
INTEM-MCF (mm)	66.4 ± 8.2	68.1 ± 6.5	*P* = .56
HEPTEM-CT (sec)	170.4 ± 19.9	197.4 ± 76.5	*P* = .13
HEPTEM-CFT (sec)	65.5 ± 17.6	71.5 ± 32.1	*P* = .49
HEPTEM-MCF (mm)	66.1 ± 6.6	67 ± 6.7	*P* = .73

P = significance, CT = clotting time, CFT = clotting forming time (), and MCF = maximum clot firmness, sec = seconds, T2D = type 2 diabetes, mm = millimeter.

ROTEM® hypercoagulable pattern was confirmed in a meta-analysis of 10 studies (enrolling 292 COVID-19 patients tested with viscoelastic methods), which showed that COVID-19 patients displayed hypercoagulation and fibrinolysis inhibition on VHA testing.[15] As already mentioned, Feuring et al reported an increased coagulability in patients with T2D in a previous ROTEM® analysis.[9] Considering these facts, one could hypothesize that patients with T2D and COVID-19 pneumonia should be at higher risk of thromboembolic events (compared to those without diabetes and COVID-19 pneumonia). To address this question, we designed a prospective study which aimed to assess the changes in hemostasis in patients with mild COVID-19 pneumonia using ROTEM® assay and to compare these changes in diabetic and nondiabetic individuals. Our study did not demonstrate significant differences in ROTEM® coagulation pattern (EXTEM®, INTEM® and HEPTEM® reagents were used for analysis) according to diabetes status. This implicates that T2D probably does not increase the hypercoagulation in patients with COVID-19 pneumonia. On the other hand, we were able to find several changes in measured EXTEM® and INTEM® parameters of ROTEM® analysis in patients with COVID-19 pneumonia compared to control healthy blood donors, confirming previously mentioned observations of COVID-19-related hypercoagulation.[6,13,15] Almskog et al showed that hypercoagulopathy is in patients with COVID-19 present early in mild to moderate disease, and is more pronounced in severe disease course.[16] Our study, together with previously mentioned ones, suggests that clot formation in patients with COVID-19 pneumonia is prolonged; nevertheless, clots rapidly increase their strength and have greater overall strength than clots of healthy individuals. In our best knowledge, this is the first study specifically examining the impact of T2D on ROTEM®-tested coagulation in patients with mild COVID-19 pneumonia. On contrary, Calvisi et al previously in a prospective analysis of 180 hospitalized patients with COVID-19 pneumonia[17] reported that diabetes/stress

hyperglycemia was associated with higher risk of thromboembolism (arterial and venous). In this study, patients with diabetes/stress hyperglycemia had increased inflammation, higher D-dimer levels, and lower antithrombin III activity. ROTEM® analysis was not performed in this study. This observation does not correspond with our results of no significant impact of T2D on COVID-19-related hypercoagulation. Right now, there is no satisfactory explanation of these differences. However, the observation might be explained by the complexity of thrombosis itself. Hypercoagulation is just a single risk factor for thrombosis, and our study was focused just on this single risk factor. T2D is associated with several other risk factors for thrombotic events, such as higher risk of immobilization, pro-inflammation, platelet dysfunction and diffuse vascular damage.[18] All these diabetes-related abnormalities might aggravate the risk of thrombosis and explain higher incidence of thrombotic events observed among COVID-19 patients with diabetes/stress hyperglycemia by Calvisi et al. Another possible explanation is that stress hyperglycemia could act as a marker, rather than as a direct contributor of an increased risk of COVID-19-related thrombosis. Calvisi et al[17] reported an increased inflammation and tissue damage circulatory markers in those with diabetes/stress hyperglycemia. In our study, no significant differences were found in inflammatory markers between T2D and nondiabetic individuals. Thus, increased risk of thrombosis might be explained by increased tissue damage (and stress hyperglycemia could reflect this increased tissue damage). Nevertheless, further studies are needed for final clarification of this issue.

The major strength of this observation is that we performed examinations in order to exclude undiagnosed diabetes, and that compared subgroups of patients with and without diabetes did not differ significantly in baseline demographics, concomitant antithrombotic and other medications, factors which could possibly affect the results. In addition, the possible differences in coagulation driven from effect of heparin administration (as a standard of care in COVID-19 patients) between diabetic patients and nondiabetic individuals were in our study excluded with HEPTEM® analysis, and this could not be performed in a previous report published by Almskog et al.[16] In our observational study, we compared patients with mild COVID-19 pneumonia with and without T2D, but we excluded patients with severe COVID-19 pneumonia who required hospitalization at ICU which added additional data in those with un-severe disease course, but could be considered as a possible limitation of our study. Another limitation is a small sample size, and a small portion of enrolled patients continued with established aspirin therapy during hospitalization. Small sample size is generally the major limitation of all the available VHA studies on COVID-19 coagulation. The meta-analysis of 10 previously published studies included only 292 individuals tested with VHA.[15] The interruption of chronic antithrombotic therapy is not recommended in patients with un-severe COVID-19 infection; therefore, patients admitted on chronic aspirin continued with medication according to current recommendations. Although aspirin therapy could, in theory, impact the ROTEM® parameters,[19] there were no significant differences in this therapy between T2D and nondiabetic patients, and it is unlikely that aspirin alone significantly affected our ROTEM® testing, as the sensitivity of standard ROTEM® for drug-induced platelet dysfunction is low.[20] Additionally, we did not perform ROTEM® analysis with FIBTEM® reagent to assess fibrin polymerization in a functional way, and healthy blood donors enrolled in the control group were slightly younger compared to controls. Considering these limitations, our results should be interpreted with caution, and should be definitely confirmed in future studies on larger patient samples.

5. Conclusions

Our study demonstrated significant changes in ROTEM® coagulation pattern in patients with mild COVID-19 pneumonia,

but did not confirm the impact of T2D on hemostatic state in patients with mild COVID-19 pneumonia. Based on possible limitations of our analysis, further studies will be needed to confirm our results.

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Author contributions

T.B., M.S., and I.Š. designed the study; T.B. and M.S. drafted the manuscript; I.Š. supervised laboratory analysis, collected, analyzed, and interpreted the laboratory data; M. Sch. and J.J. collected, analyzed, and interpreted the clinical data and performed the literature search; J.Š., P.K., and M.M. revised the manuscript critically. All the authors have read and approved the final version of the manuscript. All the authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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