International Journal of Cardiology Congenital Heart Disease 8 (2022) 100383

Contents lists available at ScienceDirect

International Journal of Cardiology Congenital Heart Disease

journal homepage: www.journals.elsevier.com/international-journal-of-cardiology-congenital-heart-disease

Point-of-care HEMOstasis in children with congenital heart disease, the POCHEMO study: Rotational thromboelastometry and impedance aggregometry in children with cyanotic and non-cyanotic congenital heart disease☆

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ARTICLE INFO

Keywords:
Aggregometry
Congenital heart disease
Cyanosis
Hemostasis
Thromboelastometry

ABSTRACT

Children with cyanotic congenital heart diseases have a higher risk of bleeding or thrombosis. Rotational thromboelastometry, using tissue factor (EXTEM), a contact activator (INTEM), or cytochalasin (FIBTEM), assesses coagulation by determining the time to initiation of clotting (CT) and clot firmness (MCF), including platelet-fibrin-interaction. This study aimed to evaluate rotational thromboelastometry and whole blood impedance aggregometry in cyanotic congenital heart diseases (CCHD) compared with a control group without chronic cyanosis (NCHD) in a pediatric cohort. We prospectively included 200 patients (60 CCHD, 140 NCHD). Oxygen saturation in CCHD was 76% [70–85], and 98% [97−100] in NCHD ($p < 0.00001$). Hemoglobin and hematocrit were significantly higher in CCHD; platelet count was significantly lower in the same group. Platelet aggregation was under normal range in 77% of CCHD after triggering with thrombin-receptor activating protein. Rotational thromboelastometry showed significantly longer clotting times and reduced clot firmness in both EXTEM and INTEM tests. FIBTEM clot firmness was also significantly reduced. In children with CCHD, a moderate inverse correlation was found between platelet count and hematocrit, with a stronger correlation after one year of age ($r = - 0.58$, $p < 0.00001$). Significant correlations were found between hematocrit, rotational thromboelastometry parameters, and impedance aggregometry parameters, so as for platelet count—the strongest correlation in CCHD after one year of age. In conclusion, according to rotational thromboelastometry and impedance aggregometry, children with CCHD present relevant hypocoagulable disorders related to cyanosis duration, but no data demonstrate hypercoagulability.

1. Introduction

Both thromboembolic and bleeding complications are significant concerns in children with cyanotic congenital heart disease (CCHD). Various coagulation abnormalities have been suggested, such as thrombocytopenia, platelet dysfunction, decreased (impaired liver function or vitamin K deficiency) or increased production of coagulation factors and primary fibrinolysis, all attributed to chronic hypoxemia and consecutive erythrocytosis and hyperviscosity [1–4].

Activated Partial Thrombin Time (aPTT), prothrombin time (PT), fibrinogen, and platelet count are routine laboratory screening tests for high bleeding risk. These tests have several weaknesses; they represent the hemostasis components' quantitative measurements but poorly correlate with the speed of clot formation or its quality (strength). They provide a weak estimate of the bleeding's risk and limited information regarding potential interventions [5].

Rotational Thromboelastometry (ROTEM®) or Thromboelastography (TEG®) are investigations of hemostasis based on whole blood

☆ All the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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https://doi.org/10.1016/j.ijcchd.2022.100383
Received 11 June 2021; Received in revised form 14 April 2022; Accepted 21 April 2022
Available online 27 April 2022

viscoelastic changes during coagulation. Recent innovations have improved their utility and made them suitable for managing bleeding during and after surgery in adult patients [6,7]. Rotational thromboelastometry provides viscoelastic testing of hemostasis in whole blood. It allows for the simultaneous evaluation of the different components involved in clot formation (plasma factors with contact activation and tissue factor activation, platelets, fibrinogen, and fibrinolysis) [8]. This analysis covers the entire process of whole blood coagulation, from the formation of the first fibrin strands over the clot's maximum firmness until its lysis.

The latest generation devices enable to combine analysis of ROTEM® with impedance aggregometry (ROTEM platelet®), which allows a targeted analysis of platelet function. Preliminary information is available in 10 min at the bedside.

These tests are not used routinely in children due to a lack of data. Nevertheless, some reference values have been published in healthy children [9,10], and more recently for children with congenital heart disease (CHD) [11].

This study aims to compare the coagulation profile of children with cyanotic and non-cyanotic congenital heart disease by rotational thromboelastometry and impedance aggregometry and to identify specific coagulopathy, platelet dysfunction in cyanotic children, and the impact of age (i.e., duration of cyanosis on the same parameters).

2. Method

2.1. Study protocol

This is a single-center, prospective observational study conducted in a tertiary pediatric care center. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the regional Ethics Committee. Written informed consent was obtained from parents, or legal surrogates of all children included. Recruitment aimed for 200 participants.

Inclusion criteria were patients younger than 16 years old, with a CHD, and undergoing a procedure requiring venous or arterial line insertion (cardiac surgery or catheterization). Exclusion criteria were lack of informed written consent, any congenital or acquired hemostatic disorder, oral anticoagulation within two days, and heparin anticoagulation within 6 h, or antiaggregation therapy within ten days before the procedure. We collected data on demographics, disease, and medical history.

All participants had standard laboratory analyses, including hemoglobin and hematocrit level, platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen concentration. Rotational thromboelastometry and impedance aggregometry were performed simultaneously with the same blood sample.

Cyanosis was defined by congenital heart disease with right-to-left shunt and a baseline arterial saturation of less than 90% under room air, determining the CCHD group (cyanotic) and the NCHD (non-cyanotic congenital heart disease group, control). *Blood sampling.*

Blood was obtained during anesthesia and before heparin administration, through either arterial line or central venous line. EDTA tube (S-Monovette® 1.2 ml, 1.6 mg EDTA/ml, SARSTEDT AG & Co., Nümbrecht, Germany) was used for the full blood count. Two citrated tubes (S-Monovette® 1.4 ml, 9NC: 0.106 mol/l, SARSTEDT AG & Co., Nümbrecht, Germany) were used for ROTEM® and standard coagulation tests, respectively.

3. Standard analyses

Tubes for blood count and standard coagulation test were immediately sent to the central laboratory of our hospital. Haemoglobin, hematocrit level, and platelet count were obtained with semiconductor laser flow cytometry. Prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen concentration were analyzed with nephelometry.

4. Rotational thromboelastometry

Analyses were performed on the ROTEM® Whole Blood Haemostasis System Type Delta and ROTEM platelet® Whole Blood Impedance Aggregometry Module (Axon Lab AG, 1052 Le Mont-sur-Lausanne, Switzerland). Following a defined operating protocol, five specially trained investigators performed the procedure: after sampling, citrated tubes were gently agitated and processed within 15 min. Single-use reagents were used to minimize manipulations and to ensure consistent results. For ROTEM®, blood was separated into three aliquots of 0.3 ml and then mixed with three specific powdered reagents in ready-to-use vials; it allows to measure the three usual pathway after recalcification: 1. activation with tissue factor (EXTEM), 2. activation with partial thromboplastin phospholipid (INTEM) or 3. activation with additional platelet inhibition by cytochalasin (FIBTEM). After that, aliquots were pipetted in a cup, which was lifted to contact the rotating pin.

5. Impedance aggregometry

The ROTEM® platelet assessed platelet function. This recently added module of the ROTEM® system measures impedance aggregometry in whole blood. From the same citrated tube, 0.2 ml whole blood was pipetted and diluted in a cuvette containing a stirring bar and electrodes. An impedance baseline was determined for 3 min. After activation by the aggregating agent, Thrombin receptor-activating protein (TRAP-TEM), platelets started to aggregate. The increase of the electrical impedance was measured for 6 min, directly proportional to the extent of platelets involved in coating the electrodes by aggregation. Electrical impedance is expressed in Ohm (Ω).

6. Parameters

Based on the existing literature [9,12–15], we focused the analysis on the more useful parameters: clotting time (CT, s), clot formation time (CFT, s), maximum clot firmness (MCF, mm), and maximum lysis (ML, %). For fibrinogen activity, the MCF was recorded.

For platelet function, the recommended parameters were registered: A6 (amplitude at 6 min, W), MS (maximum speed, W/min), and AUC (area under the curve, Ω*min).

7. Statistical methods

Data are presented using methods of descriptive statistics. All data were tested for normality and based on the data's non-parametric nature: continuous values were expressed as median [interquartile range] and compared using Wilcoxon rank-sum (Mann-Whitney) tests. For categorical variables, values were presented as number (%), and comparisons were made using Chi-square tests.

All statistical analyses were performed using STATA 16 (STATA Corp., College Station, Texas, USA). A p-value of <0.05 was considered significant.

8. Results

During the study period, 204 children were eligible. Three legal representatives declined consent, and one died before surgery, resulting in 200 children included in the study. SpO2 was inferior to 90% in 60 children (30%). Age and growth parameters were similar in both groups. Male/female ratio was 1.1 (boys 52.5%). Two patients had a history of bleeding, both being severely cyanotic. Five patients were on oral anticoagulation, in all the treatment was stopped for a minimum of five days before inclusion. Demographic data and laboratory results are summarised in Table 1.

Standard laboratory tests for blood count and coagulation function

Table 1
Demographic characteristics in control and cyanotic groups.

	Control (n = 140)	CCHD (n = 60)	*p-value*
Sex, n (%)			0.643
Female	68 (49)	27 (45)	
Male	72 (51)	33 (55)	
Age (y)	3.8 [0.9–7.4]	3.1 [1.3–4.3]	0.091
Age <1 year, n (%)	37 (26)	15 (25)	0.56
Weight (kg)	14.0 [7.9–23.0]	11.6 [8.9–15.2]	0.062
Height (m)	0.97 [0.70–1.25]	0.91 [0.73–1.00]	0.071
Body surface area (m^2)	0.60 [0.38–0.88]	0.54 [0.41–0.65]	0.069
Diagnostic, n (%)			**< 0.001**
L-R shunt	69 (49.3)	0 (0.0)	
LVOTO	21 (15.0)	0 (0.0)	
RVOTO	34 (24.3)	39 (65.0)	
Univentricular physiology	2 (1.4)	12 (20.0)	
Other	14 (10.0)	9 (15.0)	
History of bleeding, n (%)	0 (0)	2 (3.3)	**0.03**
HB (g/L)	117.0 [105.0–128.0]	147.5 [136.5–176.5]	**< 0.001**
HTC (%)	35.0 [32.0–38.0]	45.0 [41.0–56.0]	**< 0.001**
PT (%)	80.0 [75.0–90.0]	75.0 [65.0–85.0]	**< 0.001**
aPTT (s)	34 [31–38]	34 [31–40]	0.970
Platelet count (x10^9/L)	317 [237–386]	285 [174–392]	**0.045**
Fibrinogen (g/L)	2.0 [1.8–2.4]	2.2 [1.8–2.4]	0.784

Continuous variables are presented as median and interquartile range [IQR]. Categorical variables are expressed as number and proportion N(%). The cyanotic group defined as SpO2 <90%. CCHD, cyanotic congenital heart disease; HB, hemoglobin; HTC, Hematocrit; PT, prothrombin time; aPTT, activated partial thromboplastin time; RVOTO, right ventricular outflow tract obstruction; LVOTO, left ventricular outflow tract obstruction.

showed significant differences between CCHD and NCHD children except for the values of aPTT and fibrinogen. Cyanotic children had higher values of haemoglobin (147.5 [136.5–176.5] vs 117.0 [105.5–128.0] g/L; $p < 0.001$) and hematocrit (45.0 [41.0–56.0] vs 35.0 [32.0–38.0] %; $p < 0.001$).

PT values were lower in CCHD patients (median 75 [65–85] vs 80 [75–90] %; $p < 0.001$) as well as platelets count (285 [174–392] vs 317 [237–386] x10^9/L; $p < 0.045$). When we compare CCHD according to age, infants (<1 year) had lower haemoglobin (135 [126–144] vs 154 [141–184] g/L; $p = 0.0013$), hematocrit (39 [37–44] vs 49 [43–58] %; $p = 0.0001$) and fibrinogen concentration (1.9 [1.7–2.3] vs 2.3 [2.0–2.4] g/L; $p = 0.044$) than older children with CCHD. Platelets count and aPTT were higher in CCHD infants compared to CCHD older children with respectively 365 [285–525] vs 241 [158–352] x10^9/L; $p = 0.0047$ and 44 [32–49] vs 33 [30–36] s; $p = 0.008$. PT was not different in both group of CCHD.

Rotational thromboelastometry (Fig. 1) showed significantly longer clotting times in EXTEM CT: 57.0 [52.0–65.5] vs 54.0 [50.0–60.0] s, $p < 0.008$; but no significant difference in INTEM CT. A reduced clot firmness (EXTEM MCF: 57.0 [46.0–64.0] vs 61.0 [58.0–66.0] mm, $p < 0.001$; INTEM MCF: 60.0 [52.0–65.0] vs 63.0 [60.0–68.0] mm; $p < 0.001$) in the CCHD group compared with NCHD. MCF in FIBTEM was also significantly reduced (8.0 [6.0–11.0] vs 12.0 [9.0–14.0] mm, $p < 0.001$). In older children with CCHD rotational thromboelastometry showed prolonged clotting time in EXTEM and INTEM pathway, so as reduced clot firmness in all pathways (EXTEM, INTEM and FIBTEM), when compared to infants with CCHD.

Impedance aggregometry (Fig. 1) showed significant lower platelet aggregability in the CCHD versus the NCHD group: platelet aggregation was below the lower limit of the reference range (control group) in 77% after thrombin-receptor activating protein TRAPTEM AUC (63.5 [39.0–98.5] vs. 104.0 [81.0–122.0] Ω min, $p < 0.001$).

In CCHD patients, moderate inverse correlation was found between platelet count and erythrocytes ($r = -0.58$, $p < 0.0001$). Hematocrit correlated positively with EXTEM CT ($r = 0.6$, $p < 0.0001$) and inversely with EXTEM MCF ($r = -0.76$, $p < 0.0001$). Within INTEM parameters, there was no significant correlation between CT and hematocrit ($r = 0.18$, $p = 0.18$) and a strong inverse correlation with MCF ($p = -0.75$, $p < 0.0001$). FIBTEM MCF ($r = -0.64$, $p < 0.0001$) also correlated inversely with hematocrit (Fig. 2). A significant inverse correlation was also found with impedance aggregometry parameters: TRAPTEM AUC ($r = -0.69$, $p < 0.0001$). In older children with CCHD these correlation were even stronger, hematocrit correlate positively with EXTEM CT ($r = 0.61$, $p < 0.0001$) and INTEM CT ($r = 0.46$, $p = 0.0015$), inversely with EXTEM MCF ($r = -0.81$, $p < 0.0001$), INTEM MCF ($r = -0.82$, $p < 0.0001$) and FIBTEM MCF ($r = -0.67$, $p < 0.0001$). There was a strong inverse correlation between hematocrit and platelets aggregation TRAPTEM AUC ($r = -0.7$, $p < 0.0001$) (Table 2).

In CCHD patients, platelet count correlated positively with EXTEM MCF ($r = 0.71$, $p < 0.0001$), INTEM MCF ($r = 0.73$, $p < 0.0001$) as well as with FIBTEM MCF ($r = 0.47$, $p = 0.0002$). A significant inverse correlation was found between platelet count and EXTEM CT ($r = -0.47$, $p = 0.0001$) (Fig. 3). A positive correlation was also found between thrombocytes and TRAPTEM AUC test ($r = 0.61$, $p < 0.0001$). In children with longer period of cyanosis the correlation between platelets count and rotational thromboelastometry, impedance aggregometry parameters were positive with EXTEM MCF ($r = 0.65$, $p < 0.0001$), INTEM MCF ($r = 0.68$, $p < 0.0001$), FIBTEM MCF ($r = 0.45$, $p = 0.0022$) and TRAPTEM AUC ($r = 0.55$, $p = 0.0001$). The correlation was negative with EXTEM CT ($r = -0.51$, $p = 0.0004$) and INTEM CT ($r = -0.43$, $p = 0.0035$) (Table 2).

9. Discussion

To our knowledge, this is the first large prospective study on hemostasis, which compares children with cyanotic and non-cyanotic congenital heart disease, using functional analysis of clot formation with rotational thromboelastometry and platelet function with impedance aggregometry (ROTEM platelet®).

The dynamic analysis of the hemostatic process by rotational thromboelastometry and impedance aggregometry performed in whole blood shows that children with CCHD have a global hypocoagulable state compared to children with NCHD. Activation of coagulation is delayed, clot firmness and platelet function are decreased. The coagulation process seems disturbed and associates coagulation factors deficiency, polymerization disorders, and platelet dysfunction. Older children with CCHD have higher hematocrit, and with its rheological changes, a stronger alteration in coagulation and platelet function than infants with CCHD. Rotational thromboelastometry demonstrates that the progressive increase of hematocrit impacts on clotting time (prolongation) and maximal clot firmness (diminution) after activation with tissue factor (EXTEM), partial thromboplastin phospholipid (INTEM), or additional platelet inhibition by cytochalasin (FIBTEM). Identically, the progressive increase of the hematocrit with the cyanosis duration evolves inversely with the platelet's function and counts.

Chronic hypoxemia and reduced tissue oxygenation in CCHD patients lead to erythrocytosis to increase oxygen transport. Resulting hyperviscosity probably play an essential role in the pathogenesis of CCHD coagulopathy. Platelet activation and endothelial dysfunction are increased in response to high shear stress, leading, in association with hyperviscosity, to an increased risk of thrombosis [16–18]. The resulting decrease in plasma volume leads to a reduction in multiple coagulation factors, including platelets. Zabala & al suggest that thrombocytopenia in CCHD patients is related to platelet activation, platelet consumption, and decreased production [19]. All these factors lead to an increased risk of bleeding, particularly during or after surgery. The higher the degree of erythrocytosis, the greater the "coagulopathy" found [20]. This may be only an adaptive protective balance against the risk of thrombosis secondary to hyperviscosity. Our data do not suggest an increased risk for thrombosis in CCHD children, but rotational thromboelastometry or

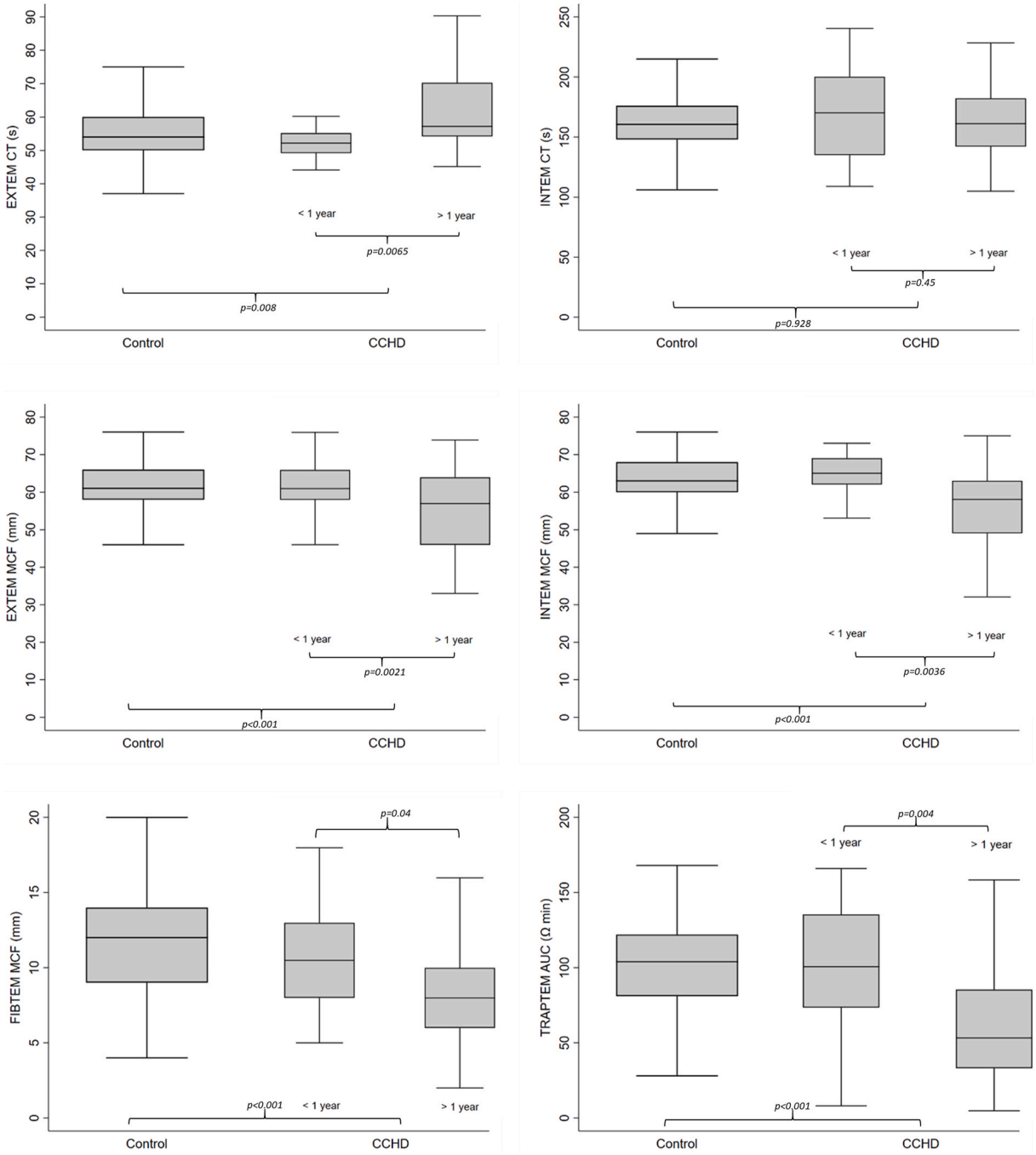

Fig. 1. Box plot of rotational thromboelastometry and impedance aggregometry in control and cyanotic groups. Cyanotic group according to age. CCHD: cyanotic congenital heart disease.

impedance aggregometry are not primarily designed to detect hypercoagulable states.

Platelet dysfunction is generally believed to play a role in this increased risk of bleeding in the CCHD population [17,19]. Impedance aggregometry is a point-of-care technique, requiring a small amount of blood, feasible in children [20]. Impedance aggregometry has been used on multiple devices, using similar principles [2,10,11,20–22]. Our data indicate that platelet function is markedly impaired in CCHD children compared to NCHD, and this impairment increases with the duration of cyanosis. Hematocrit is strongly correlated with this platelet dysfunction, suggesting that hypoxemic erythrocytosis alters platelet function. Despite statistical correlation with platelet count, it has to be highlighted that both groups have a median normal absolute platelet count. Thus, platelet dysfunction seems not primarily attributable to thrombocytopenia. These data are congruent with the evaluation of hemostasis in adult patients with cyanotic congenital heart disease [15].

Furthermore, children with CCHD reveal a hypocoagulable state on the ROTEM profile compared to NCHD. This state is even more pronounced in older children with CCHD.

CT is increased in EXTEM and with less extend in INTEM, suggesting that activation of coagulation by tissue thromboplastin (tissue factor) is more impacted than activation by the contact phase; this could mean that coagulation factors from the extrinsic system (in particular factor VII) may be deficient. Clot initiation (CT and CFT) is significantly increased and associated with decreased MCF in EXTEM and normal MCF in INTEM. This suggests that clot formation is abnormal due to

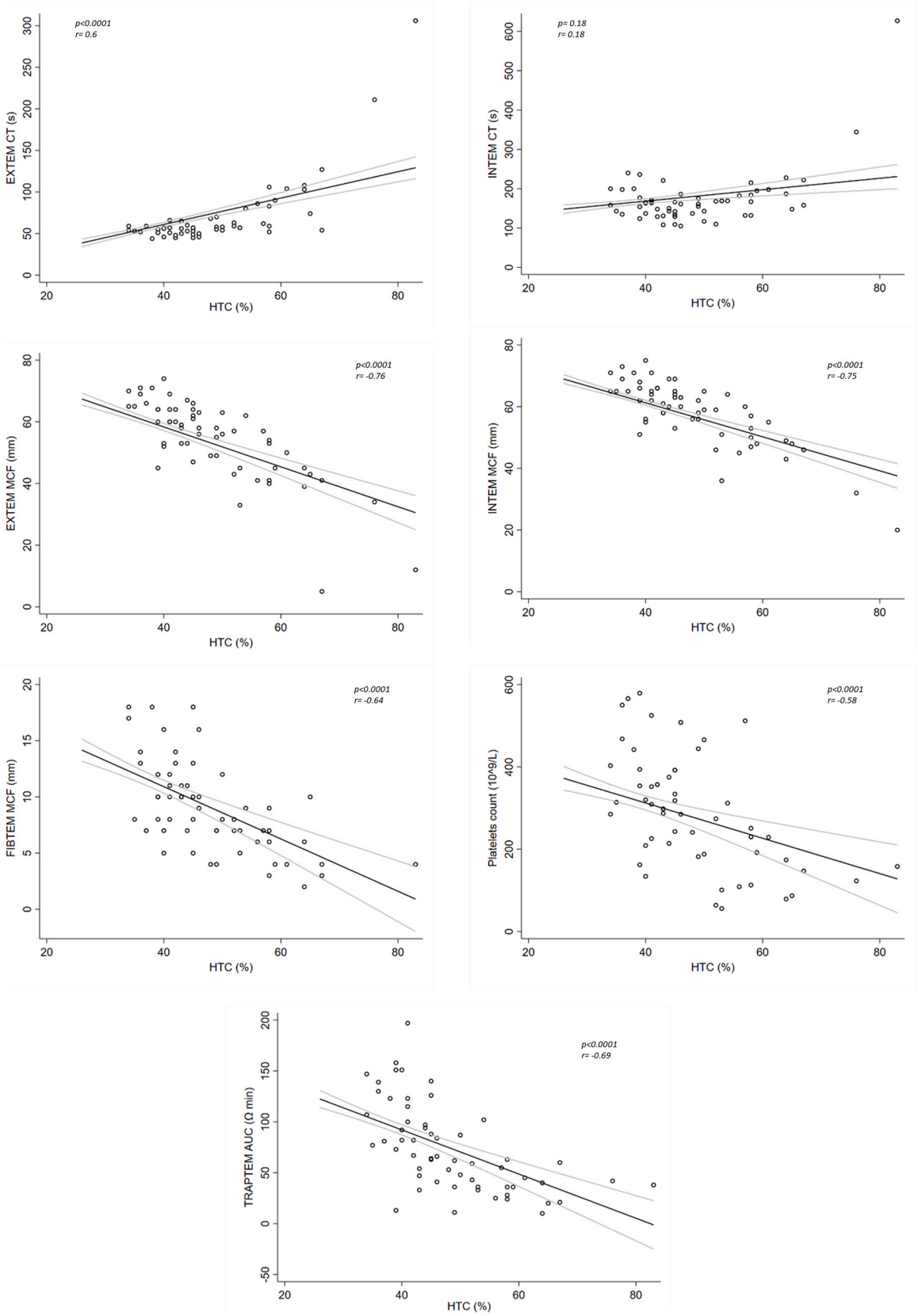

Fig. 2. Spearman's Correlation between rotational thromboelastometry, impedance aggregometry parameters and hematocrit (HTC) in cyanotic congenital heart disease group (CCHD). EXTEM, activation with tissue factor; INTEM, activation with partial thromboplastin phospholipid, FIBTEM, activation with additional platelet inhibition by cytochalasin. CT, clotting time; MCF, maximum clot firmness. TRAPTEM, thrombin receptor-activating peptide. AUC, area under the curve.

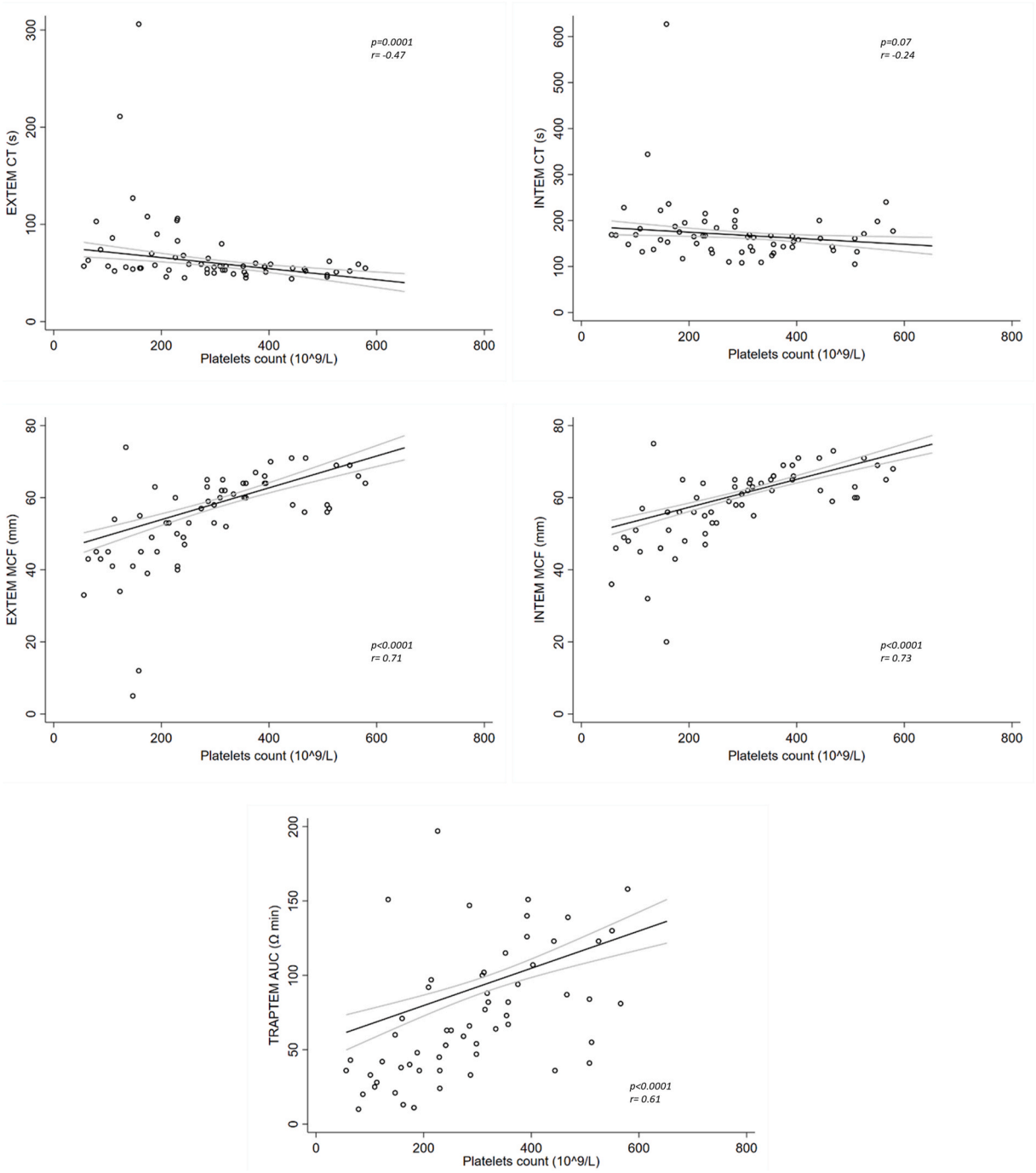

Fig. 3. Spearman's Correlation between rotational thromboelastometry, impedance aggregometry parameters and platelet count in cyanotic congenital heart disease group (CCHD). EXTEM, activation with tissue factor; INTEM, activation with partial thromboplastin phospholipid, FIBTEM, activation with additional platelet inhibition by cytochalasin. CT, clotting time; MCF, maximum clot firmness. TRAPTEM, thrombin receptor-activating peptide. AUC, area under the curve.

fibrin polymerization disorder. The results of FIBTEM support this consideration (decrease MCF in CCHD compared to NCHD).

Coagulation abnormalities in CCHD have been described since the middle of the last century. Many studies have reported coagulation disorders as thrombocytopenia and platelet dysfunctions, coagulation factors deficiencies, increased fibrinolysis and disseminated intravascular coagulation [2–4,18]. Currently, the specific disorders of hemostasis in this population are not entirely understood. These coagulation abnormalities expose children and adults with CCHD to hemostasis complications, including increased risk of both thrombosis and bleeding. However, our data do not highlight any factor that favor thrombosis, like Pujol & *al* study in adults with cyanotic congenital heart disease [15].

There is a discrepancy between the fibrinogen determination in the laboratory and FIBTEM results. For both NCHD and CCHD, fibrinogen values are in the low but normal range, while the FIBTEM profile suggests low fibrinogen or fibrinogen polymerization disorder. We hypothesize that FIBTEM is much more sensitive to clot polymerization disorders when conventional laboratory assays mainly inform about the total amount of fibrinogen as suggested by Jensen & al [20].

The present study has some limitations. The first one is that we did not adjust the citrate level in the tubes for children with high hematocrit. According to the literature, there are alterations of hemostasis by

rheological changes related to erythrocytosis. It has also been suggested that, for patients with high hematocrit, alteration of hemostasis may be caused by the absence of adjustment of the citrate content of the sampling tube [1–4]. Nonetheless, the study's scope was to remain in a "real-life" situation in which POC systems have been demonstrated effective, leading to a more targeted intervention and possibly sparing blood products. The second limitation is that the results' reproducibility and quality could be questionable since handling the sample requires nursing or medical staff's competence and availability. In this study, the rate of analytic failure is remarkably low. Investigators were restricted in number, specially trained, and not in charge of the patient while processing the samples to guarantee the most homogenous results. These settings could be challenging to reproduce [6].

In conclusion, this study shows consistent data indicating that children with CCHD have abnormal coagulation parameters measured by rotational thromboelastometry and impendence aggregometry. Hypoxia-induced erythrocytosis and fibrinogen dysfunction are the most likely incriminated factors for altered thromboelastometry and aggregometry, leading to a hypocoagulable situation that increases with the duration of the cyanosis. Standard laboratory tests of coagulation do not demonstrate significant changes and are not useful in assessing the risk of coagulopathy in children with cyanotic congenital heart disease. Although it is well demonstrated that these children have an increased risk of thrombosis, data from rotational thromboelastometry and impendence aggregometry do not demonstrate any pro-coagulant factor. Physicians caring for these children should be aware of these specificities and favor hemostasis evaluation with these techniques when bleeding occurs.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ijcchd.2022.100383.

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