Cardiology in the Young

cambridge.org/cty

Impact of platelet population behaviours in patients undergoing the Glenn procedure

Ergin Arslanoglu[1], Eylem Tuncer[1], Nihat Cine[1], Kenan Abdurrahman Kara[1], Babürhan Ozbek[1], Abdullah Arif Yılmaz[1], Fatih Tomrukcu[1], Omer Savluk Faruk[2], Fatma Ukil[2] and Hakan Ceyran[1]

[1]Pediatric Cardiovascular Surgery Department Kartal Kosuyolu High Speciality Educational and Research Hospital, İstanbul, Turkey and [2]Anaesthesia and Reanimation Department Kartal Kosuyolu High Speciality Educational and Research Hospital, İstanbul, Turkey

Original Article

Cite this article: Arslanoglu E, Tuncer E, Cine N, Kara KA, Ozbek B, Yılmaz AA, Tomrukcu F, Savluk Faruk O, Ukil F, and Ceyran H (2021) Impact of platelet population behaviours in patients undergoing the Glenn procedure. *Cardiology in the Young* **31**: 1675–1679. doi: 10.1017/S104795112100086X

Received: 18 January 2021
Revised: 12 February 2021
Accepted: 12 February 2021
First published online: 12 April 2021

Keywords:
Congenital cardiac surgery; Glenn procedure; pulmonary artery hypertension; mean platelet volume; platelet distribution width; functionally univentricular heart

Author for correspondence:
Kenan Abdurrahman Kara, MD, Associate Professor, Pediatric Cardiovascular Surgery Department Kartal Koşuyolu High Speciality Educational and Research Hospital, Denizer street no:2 post code:34865 Kartal İstanbul, Turkey. Tel: +905300655225.
E-mail: kenankaradoc@gmail.com

Abstract

Pulmonary pressure is one of the most important parameters in the postoperative follow-up of patients who have undergone the Glenn procedure. Platelet activation markers, which are inexpensive and easily accessible blood count parameters, have been shown to be associated with the aetiology and pathogenesis of primary pulmonary artery hypertension. We examined the relationship between platelet activation markers and pulmonary pressures in the early post-operative period of patients who underwent the Glenn procedure.

Eighty-five patients who underwent the Glenn procedure in our clinic between January 2011 and March 2020 were included in the study retrospectively. Fifty-one patients were male and 34 were female, and age varied from 4 to 416 months, with a mean of 28.64 ± 51 months.

Patients with increased pulmonary blood flow on palliation before Glenn surgery had higher mean platelet volume values. However, no correlation was found between pulmonary pressures and platelet activation markers in the early postoperative period.

There was not similar study evaluating platelet activation markers in the paediatric age group before and after postoperative Glenn surgery in the literature. Therefore, even if platelet activation markers provide information about the pulmonary bed, they may be misleading due to other reasons that trigger bleeding and inflammatory processes in the early postoperative period.

The Glenn procedure is a cardiac intervention that can be safely used in the initial phase of palliation in various types of single ventricle defects.

Although primary pulmonary artery hypertension pathogenesis is multifactorial, the most important factor in the pathogenesis is endothelial dysfunction. However, it may also occur due to vasoconstriction, thrombosis, and pulmonary artery remodelling.[1–3] The development of pulmonary artery hypertension is not only associated with inflammatory cells and their activation, but also other cell types, including fibroblasts, endothelial cells, smooth muscle cells, platelets, and other shaped blood elements.[4] Previous studies have shown that there is a correlation between pulmonary arteriole characteristics and platelets, which has been, in turn, associated with the development of primary pulmonary artery hypertension.[5]

Mean platelet volume, platelet distribution width, platelet size and variability, and plateletcrit, total mass of platelets in the blood are defined as markers of platelet activation. Physiologically, increases in mean platelet volume and platelet distribution width value are followed by elevated platelet activation which leads to easier aggregation of large platelets and adherence to the endothelium. Elevated mean platelet volume values are considered an independent risk factor for coronary and peripheral artery disease. With the same mechanism, increased platelet distribution width and mean platelet volume values in the aetiology of pulmonary artery hypertension mean platelet volume are thought to cause pulmonary arterial hypertension through triggering of platelet aggregation.[6,7] Furthermore, previous studies have shown that patients with idiopathic pulmonary hypertension have higher mean platelet volume than the normal population, and it has been suggested that thrombocyte activation directly plays a role in the pathogenesis of pulmonary artery hypertension.[8,9]

In our study, we investigated the relationship between platelet activation and postoperative characteristics of patients who underwent Glenn surgery, by comparing platelet activation markers and pulmonary pressure values in single ventricle patients.

Material and methods

Eighty-five patients who underwent the Glenn procedure in our clinic between January 2011 and March 2020 were included in the study. Patients' characteristics, such as gender, age, weight, operation date, cross clamp duration, total cardiopulmonary by-pass time, and central

Table 1. Measurement averages

	Mean ± SD	Min–max (Median)
Age (Month)	28,64 ± 51	4–416 (11)
Weight (Kg)	10,57 ± 9,08	4,8–80 (8)
CPB duration (minutes)	70,42 ± 29,49	9–172 (62,5)
PDW preop (fL)	17,3 ± 4,28	14,6–55 (16,6)
MPV preop (fL)	8,24 ± 1,2	5,97–11,4 (8,1)
PLT preop (10^3 uL)	308,42 ± 116,93	85–682 (285)
PCT preop (%)	0,25 ± 0,1	0,08–0,53 (0,23)
PDW postop-1 (fL)	18,19 ± 6,44	15,4–61 (17)
MPV postop-1 (fL)	8,16 ± 1,57	1,79–13,8 (8)
PLT postop-1 (10^3 uL)	175,77 ± 79,5	27–524 (164)
PCT postop-1 (%)	0,14 ± 0,06	0,03–0,36 (0,13)
PDW postop-2 (fL)	18,22 ± 7,16	16–69 (16,9)
MPV postop-2 (fL)	8,36 ± 1,09	6,4–11,9 (8,2)
PLT postop-2 (10^3 uL)	167,58 ± 75,87	14–564 (163)
PCT postop-2 (%)	0,14 ± 0,06	0,02–0,36 (0,13)
Preop PAP (mmHg)	14,27 ± 2,83	9–24 (14)
PO1 PAP (mmHg)	13,88 ± 3,03	8–23 (14)
PO2 PAP (mmHg)	13,27 ± 3,21	7–24 (13)
PO3 PAP (mmHg)	13,11 ± 3,16	8–25 (13)
Extubation time (day)	4,62 ± 13,25	0–92 (1)
Amount of drainage on the first postoperative day (ml)	140 ± 90,94	20–500 (100)
Length of stay in ICU (day)	9,51 ± 13,87	0–92 (4)
Length of stay in ward (day)	7,22 ± 6,12	0–35 (6)

CPB = Cardiopulmonary bypass; fL = femtoliters; ICU = Intensive care unit; mL = milliliter; mmHg = millimeter of mercury; MPV = Mean platelet volume; PAP = Pulmonary arterial pressure; PCT = plateletcrit; PDW = Platelet distribution width; PLT = Total mass of platelets in the blood; PO1 = Postoperative 1st day.

venous catheter pressure values were obtained retrospectively from patient files. The platelet distribution width, platelet count, plateletcrit, and mean platelet volume values were recorded from routine complete blood count measurements. The pulmonary pressures of the patients were determined from the angiography reports of preoperative catheter measurements performed in the preoperative period and at postoperative days 1, 2, and 3. Invasive measurements were made from the central line of each patient.

The patients' Mean platelet volume (fL), plateletcrit (%), platelet distribution width (fL), total mass of platelets in the blood (10^3 uL) values measured from the preoperative haemogram were compared with the pulmonary artery pressure values during preoperative catheterization. Pulmonary artery pressure values obtained from central venous catheter on the postoperative 1st, 2nd and 3rd days were compared with Mean platelet volume, plateletcrit, platelet distribution width, total mass of platelets in the blood values obtained from haemogram on the same day.

The blood samples were obtained from central venous catheter inserted during the operation and stored in ethylenediaminetetraacetic acid-containing haemogram tubes and evaluated in the biochemistry laboratory of our center.

The operations of the patients were performed under cardiopulmonary bypass with a routine conventional median sternotomy and selective bicaval-aortic cannulation.

The NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) programme was used for statistical analysis. The study data were described with Mean, Standard Deviation, Median, Frequency, Ratio, Minimum and Maximum values. The Shapiro–Wilk test was also used to evaluate the distribution of continuous variables. The Kruskal–Wallis test was used to compare continuous variables that did not show normal distribution in three or more groups, and the Mann–Whitney U test was used for comparison of two groups. The Friedman test was used for time-bound comparison of variables between three or more groups in the presence of non-normal distribution, and the differences were determined via the Wilcoxon test. Spearman's correlation test was used assess relationships between quantitative data. Significance was evaluated at $p < 0.05$ level.

Results

Of the 85 patients included in the study, 51 were males and 34 were females. The age varied between 4 and 416 months, with an average of 28.64 ± 51 months. The weights of the patients ranged from 4.8 to 80 kg, with an average of 10.57 ± 9.08 kg. The cardiopulmonary bypass duration ranged from 9 to 172 minutes, with an average of 70.42 ± 29.49 minutes (Table 1). Patients who underwent valve repair and pulmonary reconstruction with additional cardiac pathology together with the Glenn surgery were included in the study.

It was found that 12.8% (n = 11) of the patients died and 87.2% (n = 74) were discharged. The duration of intubation in deceased patients was significantly higher than the discharged group ($p < 0.01$). The duration of stay in the intensive care unit in deceased patients was significantly higher than the discharged group ($p = 0.001$; $p < 0.01$). There was no statistically significant difference between the postoperative first day drainage values of the patients who died and were discharged ($p > 0.05$).

The preoperative platelet distribution width values of the discharged group was found to be significantly higher compared to the deceased patient group ($p = 0.04$; $p < 0.05$). The average preoperative platelet distribution width value of the discharged group was 17.43 ± 4.57, while this value was 16.44 ± 1.01 in the deceased group (Table 2).

The mean preoperative pulmonary artery pressure value of patients who died was significantly higher compared to the discharged group ($p = 0.021$; $p < 0.05$).

The mean postoperative first day pulmonary artery pressure value of the deceased group was significantly higher than the discharged group ($p = 0.001$; $p < 0.01$).

The mean postoperative second day pulmonary artery pressure value of the deceased group was significantly higher compared to the discharged group ($p = 0.001$; $p < 0.01$).

Similarly, postoperative third day pulmonary artery pressure values were significantly higher in the deceased group compared to the discharged group ($p = 0.001$; $p < 0.01$).

There was a statistically significant difference between platelet distribution width measurements by periods ($p = 0.001$; $p < 0.01$). The preoperative platelet distribution width measurements were significantly lower compared to the postop-1 and postop-2 measurements ($p = 0.001$; $p < 0.01$).

There was a statistically significant difference between Mean platelet volume measurements by periods ($p = 0.019$; $p < 0.05$).

https://doi.org/10.1017/S104795112100086X Published online by Cambridge University Press

Table 2. Comparison of platelet activation values by periods

		Preop (n = 85)	Postop-1st day (n = 85)	Postop-2nd day (n = 85)	p
PDW (fL)	Mean ± SD	17,3 ± 4,28	18,19 ± 6,44	18,22 ± 7,16	0,001**
	Min–max (Median)	14,6–55 (16,6)	15,4–61 (17)	16–69 (16,9)	
MPV (fL)	Mean ± SD	8,24 ± 1,2	8,16 ± 1,57	8,36 ± 1,09	0,019**
	Min–max (Median)	5,97–11,4 (8,1)	1,79–13,8 (8)	6,4–11,9 (8,2)	
PLT (10^3 uL)	Mean ± SD	308,42 ± 116,93	175,77 ± 79,5	167,58 ± 75,87	0,001**
	Min–max (Median)	85–682 (285)	27–524 (164)	14–564 (163)	
PCT (%)	Mean ± SD	0,25 ± 0,1	0,14 ± 0,06	0,14 ± 0,06	0,001**
	Min–max (Median)	0,08–0,53 (0,23)	0,03-0,36 (0,13)	0,02-0,36 (0,13)	

Friedman Test **p < 0,01.

The postop-2 Mean platelet volume measurements were significantly higher compared to preop and postop-1 measurements ($p = 0.001$; $p < 0.01$).

There was a statistically significant difference between total mass of platelets in the blood measurements by periods ($p = 0.001$; $p < 0.01$). Preoperative total mass of platelets in the blood values were found to be significantly higher compared to postop-1 and postop-2 measurements ($p = 0.001$; $p < 0.01$).

There was a statistically significant difference between plateletcrit measurements by periods ($p = 0.001$; $p < 0.01$). Preoperative plateletcrit measurement results were significantly higher compared to the postop-1 and postop-2 measurements ($p < 0.01$).

There was a negative and very weak significant correlation between preop platelet distribution width and postoperative first day drainage ($r = -0.235$, $p < 0.05$).

There was a positive and weak significant relationship between the amount of drainage on the first day and the duration of intensive care stay ($r = 0.280$, $p < 0.05$).

When the patients were separated according to the presence of decreased and increased blood flow, and with respect to previous operation, we found that 26 patients underwent pre-Glenn band and 59 patients underwent shunt operation. Five of the patients who underwent shunting (8.4% mortality) and band (19% mortality) died. In both of these patient groups, no statistically significant relationship was found between plateletcrit, Mean platelet volume, total mass of platelets in the blood, platelet distribution width and pulmonary pressures ($p > 0.05$) (Tables 3 and 4).

Complications were, Glenn takedown in two patients, chylothorax in three, prolonged need for ventilation (>10 days) in nine, and bleeding revision in one patient.

Discussion

Knowledge regarding the presence/absence of pulmonary hypertension, which is one of the most important determinants of mortality and morbidity in single ventricle patients, plays an important role in postoperative patient follow-up. High pulmonary artery pressure is of great importance in the decision of the Glenn operation and the prognosis after the operation.[10] It is difficult to predict whether pulmonary arterial hypertension is reversible. Its reversibility depends on the underlying pathology. Although there is no definite opinion in the literature regarding the reversibility of postoperative pulmonary artery hypertension, postoperative pulmonary artery hypertension after Glenn shunt surgery is usually reversible.[1,2]

Pulmonary vascular endothelial dysfunction in pulmonary artery hypertension can cause platelet activation and local thrombosis. In addition, systemic inflammation in pulmonary artery hypertension patients may cause platelet activation and can increase markers of platelet activation. Inflammatory response is an important feature of pulmonary artery hypertension, and increased levels of circulating cytokines, including interleukin-6, have been reported in patients with pulmonary artery hypertension and cytokine elevation has been negatively associated with survival. Cytokines such as interleukin-3 or interleukin-6 have been demonstrated to affect megakaryocytes and may lead to the production of relatively more reactive and larger platelets.[11] Therefore, increased interleukin-6 in pulmonary artery hypertension patients may cause an increase in mean platelet volume values by stimulating megakaryocytes.[12] Pulmonary pressure increase in single ventricle patients is different from primary pulmonary artery hypertension; however, the two conditions may be similar with respect to platelet characteristics. Pathogenesis of pulmonary artery hypertension may be similar to that of primary pulmonary artery hypertension, especially in patients with a single ventricle with increased pulmonary blood flow.[13,14]

In our study, when we grouped patients with respect to Glenn shunts and pulmonary bands applied at the first palliation, we found that the mean platelet volume value of the group with shunt application was higher than the value of the group with band application. We attributed this to the use of foreign body (shunt graft) in patients who underwent shunt operation and the higher inflammatory response due to the non-physiological flow dynamics of the shunt. However, we could not obtain significant statistical relationships between platelet activation markers and pulmonary pressures in either group.

In patients with cyanosis, erythropoiesis is stimulated to increase oxygen delivery to the tissues, and the number of red blood cells increases, but the number of platelets decreases. The lower the oxygen in the blood, the greater the increase in haemoglobin will be. Inversely, there will be a decrease in platelet level. Thus, haemoglobin and platelet level can indirectly provide data about the severity of cyanosis. Although the platelet count is decreased in these patients, thrombogenic events are common. Additionally, it should be noted that previous studies have associated mean platelet volume values with increased aggregation, but no significant increase in mean platelet volume values is observed among cyanotic patients.[15–17] Mean platelet volume is a simple and easy method of evaluating platelet function obtained from routine postoperative haemogram results and reflects the rate and stimulation of platelet production.[18]

https://doi.org/10.1017/S104795112100086X Published online by Cambridge University Press

Table 3. Comparison of Shunt Group Values by Periods (decreased pulmonary flow)

		Preop (n=59)	Postop-1st day (n=59)	Postop-2nd day (n=59)	p
PDW	Mean ± SD	16,89 ± 1,22	17,99 ± 5,78	18,07 ± 6,79	0,001**
	Min–max (Median)	14,6–22,6 (16,6)	15,4–61 (16,9)	16–69 (17)	
MPV	Mean ± SD	8,4 ± 1,27	8,35 ± 1,73	8,51 ± 1,17	0,102
	Min–max (Median)	5,97–11,4 (8,3)	1,79–13,8 (8,1)	6,46–11,9 (8,34)	
PLT	Mean ± SD	316,24 ± 128,59	177,47 ± 85,41	165,22 ± 80,76	0,001**
	Min–max (Median)	85–682 (285)	27–524 (164)	14–564 (161)	
PCT	Mean ± SD	0,26 ± 0,11	0,15 ± 0,06	0,14 ± 0,06	0,001**
	Min–max (Median)	0,079–0,53 (0,25)	0,03–0,36 (0,13)	0,02–0,364 (0,13)	

Friedman Test **p < 0,01.

Table 4. Comparison of Band Group Values by Periods (increased pulmonary flow)

		Preop (n = 26)	Postop-1st day (n = 26)	Postop-2nd day (n = 26)	p
PDW	Mean ± SD	18,24 ± 7,55	18,64 ± 7,85	18,57 ± 8,07	0,017**
	Min–max (Median)	15,5–55 (16,55)	16,1–57 (17)	16–58 (16,8)	
MPV	Mean ± SD	7,89 ± 0,96	7,75 ± 1,04	8,04 ± 0,81	0,108
	Min–max (Median)	6,6–9,9 (7,77)	5,78–10,7 (7,8)	6,4–9,9 (7,95)	
PLT	Mean ± SD	290,69 ± 84,3	171,92 ± 65,51	172,92 ± 64,55	0,001**
	Min–max (Median)	111–466 (283,5)	59-340 (167)	88–351 (171,5)	
PCT	Mean ± SD	0,23 ± 0,06	0,13 ± 0,05	0,14 ± 0,05	0,001**
	Min–max (Median)	0,09–0,327 (0,22)	0,04–0,234 (0,13)	0,08–0,242 (0,13)	

Friedman Test **p < 0,01.

In the study conducted by Varol et al, they showed that mean platelet volume was significantly higher in adult primary pulmonary artery hypertension patients.[8] In our study, we found no correlation between mean platelet volume and pulmonary pressures in the early postoperative period after Glenn surgery in the paediatric patient group. We attributed this to the fact that there was no change in mean platelet volume in the early postoperative period and the number of patients was limited, especially considering that primary pulmonary artery hypertension pathogenesis is a chronic process. In addition, we believe that the paediatric age of the patients in our study also affected the results.

Although platelet count and activation markers are suggestive parameters in idiopathic pulmonary hypertension, in our retrospective study, no significant relationship was found between pulmonary pressures and platelet activation markers, with regard to increased inflammation and surgical stress in the postoperative period after cardiac surgery.[1] However, in our study, platelet distribution width and mean platelet volume increased while total mass of platelets in the blood and plateletcrit decreased in the postoperative period compared to the preoperative period. We think this was due to increased inflammation and increased consumption.

Pulmonary artery hypertension that develops in the early postoperative period after Glenn shunt surgery is not only associated with inflammation and endothelial dysfunction, it has been associated with various causes and is considered a multifactorial development. The processes in the development of postoperative pulmonary artery hypertension in single ventricle patients are different from primary pulmonary artery hypertension. Therefore, platelet activation markers used in the diagnosis of primary pulmonary artery hypertension are of limited use in postoperative patients and may be misleading. In our study, the correlations between early postoperative pulmonary pressures and platelet activation markers were statistically non-significant. We believe that one of the reasons for this situation was the transfer of blood into a foreign surface (during cardiopulmonary bypass), causing formation of an inflammatory response, and consequently, altering platelet activation markers.

In conclusion, patients with pulmonary increased blood flow before Glenn surgery were found to have higher mean platelet volume values. In addition, even if platelet activation markers provide information about the pulmonary bed, they may be misleading due to other reasons that trigger inflammatory processes in the early postoperative period.

Acknowledgements. None.

Financial support. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest. None.

Ethical statement. The ethics committee approved the study protocol and all steps of the study were conducted in accordance with the principles of the Declaration of Helsinki. (2020/14/411).

References

1. Badesch DB, Champion HC, Sanchez MA, et al. Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol 54: 55–66.
2. Can MM, Tanboğa IH, Demircan HC, et al. Enhanced hemostatic indices in patients with pulmonary arterial hypertension: an observational study. Thromb Res 2010; 126: 280–282. doi: 10.1016/j.thromres.2010.06.020. Epub 2010 Aug 1. PMID: 20673969.
3. Sakao S, Tatsumi K. Vascular remodeling in pulmonary arterial hypertension: multiple cancer-like pathways and possible treatment modalities. Int J Cardiol 2011; 147: 4–12.
4. De Luca G, Venegoni L, Iorio S. Platelet distribution width and the extent of coronary artery disease: results from a large prospective study. Platelets 2010; 21: 508–514.
5. Zanjani KS. Platelets in pulmonary hypertension: a causative role or a simple association? Iran J Pediatr 2012; 22: 145–157.
6. Soydinc S, Turkbeyler IH, Pehlivan Y, et al. Mean platelet volume seems to be a valuable marker in patients with systemic sclerosis. Inflammation 2014; 37: 100–106.
7. Sansanayudh N, Anothaisintawee T, Muntham D, McEvoy M, Attia J, Thakkinstian A. Mean platelet volume and coronary artery disease: a systematic review and meta-analysis. Int J Cardiol 2014; 175: 433–440. doi: 10.1016/j.ijcard.2014.06.028. Epub 2014 Jun 28. Erratum in: Int J Cardiol. 2014 Dec 20;177(3):1145. AmmarinThakkinstian [corrected to Thakkinstian, Ammarin]. PMID: 25017904.
8. Varol E, Uysal BA, Ozaydin M. Platelet indices in patients with pulmonary arterial hypertension. Clin Appl Thrombosis/Hemostasis 2011; 17: E171–E174.
9. Can MM, Tanboga IH, Demircan HC, et al. Enhanced hemostatic indices in patients with pulmonary arterial hypertension: an observational study. Thromb Res 2010; 126: 280–282.
10. Kijima R, Sasaki O, Shinmei Y, et al. Changes in intraocular pressure in single ventricle patients after the Glenn or Fontan procedure. J Glaucoma 2019; 28: 1012–1014. doi: 10.1097/IJG.0000000000001375. PMID: 31567909.
11. Soon, E, Holmes, AM, Treacy, CM. Elevated levels of inflammatory cytokines predict survival in idiopathic and familial pulmonary arterial hypertension. Circulation 2010; 122: 920–927.
12. Debili, N, Masse, JM, Katz, A. Effects of the recombinant hematopoietic growth factors interleukin-3, interleukin-6, stem cell factor, and leukemia inhibitory factor on the megakaryocytic differentiation of CD34ş cells. Blood 1993; 82: 84–95.
13. Vizioli, L, Muscari, S, Muscari, A. The relationship of mean platelet volume with the risk and prognosis of cardiovascular diseases. Int J Clin Pract 2009; 63: 1509–1515.3.
14. Nakonechnicov S, Gabbasov Z, Chazova I, Popov E, Belenkov Yu. Platelet aggregation in patients with primary pulmonary hypertension. Blood Coagulation Fibrinolysis 1996; 7: 225–227. doi: 10.1097/00001721-199603000-00029. PMID: 8735825.
15. Matter RM, Ragab IA, Roushdy AM, Ahmed AG, Aly HH, Ismail EA. Determinants of platelet count in pediatric patients with congenital cyanotic heart disease: Role of immature platelet fraction. Congenit Heart Dis 2018; 13: 118–123. doi: 10.1111/chd.12530. Epub 2017 Sep 7. PMID: 28880458.
16. Martin-Garcia AC, Arachchillage DR, Kempny A, et al. Platelet count and mean platelet volume predict outcome in adults with Eisenmenger syndrome. Heart 2018; 104: 45–50. doi: 10.1136/heartjnl-2016-311144. Epub 2017 Jun 29. PMID: 28663364.
17. Laskine-Holland ML, Kahr WH, Crawford-Lean L, et al. The association between Cyanosis and Thromboelastometry (ROTEM) in children with congenital heart defects: a retrospective cohort study. Anesth Analg 2017; 124: 23–29. doi: 10.1213/ANE.0000000000001708. PMID: 27861436.
18. Park, Y, Schoene, N, Haris, W. Mean platelet volume as an indicator of platelet activation: methodological issues. Platelets 2002; 13: 301–306.

https://doi.org/10.1017/S104795112100086X Published online by Cambridge University Press