Cardiology in the Young

cambridge.org/cty

Original Article

Cite this article: Berganza FM, Gonzalez de Alba C, Egbe AC, Bartakian S, Brownlee J. (2018) Prevalence of aspirin resistance by thromboelastography plus platelet mapping in children with CHD: a single-centre experience. *Cardiology in the Young* **29**: 24–29.
doi: 10.1017/S1047951118000021

Received: 29 September 2016
Revised: 19 December 2017
Accepted: 26 December 2017
First published online: 3 December 2018

Key words:
Aspirin resistance; thromboelastography; platelet mapping; CHD; general cardiology

Author for correspondence:
J. Brownlee, MD, FAAP, FACC, Heart Center, Driscoll Children's Hospital, 3533 S Alameda St, Corpus Christi, TX 78411, USA.
Tel: 361 694 5086; Fax: 361 855 9518;
E-mail: John.Brownlee@dchstx.org

Prevalence of aspirin resistance by thromboelastography plus platelet mapping in children with CHD: a single-centre experience

Fernando M. Berganza[1], Cesar Gonzalez de Alba[1], Alexander C. Egbe[2], Sergio Bartakian[3] and John Brownlee[4]

[1]Department of General Pediatrics, Driscoll Children's Hospital, Corpus Christi, TX, USA, [2]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, USA, [3]Health Science Center, University of Texas, San Antonio, TX, USA and [4]Department of Pediatric Cardiology, Driscoll Children's Hospital, Corpus Christi, TX, USA

Abstract

Rationale: Aspirin resistance has been reported in up to 80% of children with cardiovascular defects undergoing surgery. Because of a patient who had embolic stroke while on therapeutic aspirin dose but in whom aspirin resistance was present on his thromboelastography platelet mapping, we chose to obtain thromboelastography platelet mapping on cardiac patients on aspirin to assess their risk. *Objectives:* This study evaluates aspirin resistance noted in these patients and their characteristics. *Methods and results:* This is a retrospective study of 25 patients taking aspirin for a month at therapeutic dose. In total, 11 female patients were enrolled. Ages in all subjects were 5 months to 27 years. A total of 19 patients had a Fontan surgery. Three had a cavopulomanary anastomosis, one had a hybrid procedure, and two had coronary anomalies. Compliance was assessed at the time of the clinic visit. Aspirin resistance was defined as platelet inhibition below 50%. Variables evaluated were level of platelet inhibition, age, body mass index, and gender.

Aspirin has been used to prevent thromboembolism in children with CHDs without conclusive evidence supporting its anti-platelet efficacy in this specific group of diseases. The effectiveness of aspirin and other anti-platelet agents has been subject to criticism related to possible resistance or biologic variability.[1]

There is an open debate about the incidence of aspirin resistance in the paediatric population. The incidence of aspirin resistance has been reported to range from 2.3 up to 80% in the medical literature through different laboratory assessments.[2,3] However, there has been a poor correlation among the different tests to measure platelet function and the prediction of thrombotic events.[1,4–8]

Even though the possible aspirin resistance and its questionable efficacy in children has raised concerns among patients and physicians, no laboratory assay has been recognised to effectively monitor aspirin therapy in children.[9] The possible causes of aspirin resistance include poor compliance, drug interaction, inadequate aspirin dose, increased turnover of platelets, genetic polymorphism of cyclooxygenase-1, and up-regulation of alternative (non-platelet) pathways of thromboxane production.[10]

Children undergoing cardiac surgery are at a higher risk for thrombosis than the general paediatric population.[11] Thromboembolic disease is a significant cause of morbidity and mortality in infants and children. Nearly 50% of infants younger than 6 months of age and 30% of older children with venous thromboembolic disease have an underlying cardiac disease.[12] Almost 8–33% of subjects will suffer from thrombosis after Fontan surgery.[12] The evidence supporting most recommendations for anti-thrombotic therapy in neonates and children remains weak and most recommendations are based on extrapolation from adults.[13,14]

Thromboelastogram plus platelet mapping (TEGPM) test has been previously proposed to function as a bedside test to assess the platelet function of adult patients taking aspirin.[15] The aim of this study is to evaluate the effectiveness of platelet therapy with TEGPM in children with CHD after being surgically repaired.

Materials and methods

Study design

The Institutional Review Board committee at Driscoll Children's hospital approved this study. A retrospective chart review was completed in 24 subjects with surgically repaired CHD and one subject with an acquired heart condition which was coronary aneurysm due to Kawasaki disease, who had had a standard TEGPM done to evaluate aspirin therapy. All of the patients

CAMBRIDGE UNIVERSITY PRESS

fulfilled the inclusion criteria of receiving aspirin therapy for more than 1 month. The aspirin dosage was 5 mg/kg/day, not to exceed 81 mg/day. The compliance of aspirin therapy was confirmed during the patient's follow-up visit. The decision to perform a thromboelastogram plus platelet mapping was done by the primary cardiologist based on evidence of previous compliance to medications.

All reviewed data included patients' charts from July, 2014 to June, 2015. A complete blood count drawn within a week from the TEGPM in sample was also extracted from the patients' charts to measure haemoglobin and platelet levels for quality control. All study patients had an echocardiogram performed within a week of their standard TEGPM test collection.

Blood sampling and thromboelastogram analysis

Thromboelastogram plus platelet mapping is a different test than simple thromboelastogram 5000, Haemonetics Corporation analyzer system (Braintree, Massachussets, United States of America). For a standard thromboelastogram®, a specimen on 1.8 cc of whole blood in 3.2% of sodium citrate was taken by phlebotomy from the patient's antecubital fossa. The sample was transported to the laboratory immediately and was allowed to sit for 15 minutes before analysis. An additional tube with 3 cc of whole blood on sodium heparin (75 units) was obtained for platelet mapping assessment.

In classical thromboelastogram®, a small cuvette of blood is slowly rotated through an arc of about 4.75°, six times per minute, to imitate sluggish venous flow and to activate coagulation. A thin probe is immersed in the moving cuvette; a clot begins to form between the probe and the side of the cuvette. The strength of the clot, among other parameters, is measured over time.[16] The Maximal Amplitude represents the strength of the clot.

The modified thromboelastogram® to assess platelet function (platelet mapping) uses four channels to detect the effects of antiplatelet therapy acting via the arachidonic acid and adenosine diphosphate pathways.[15–17] The samples were run until Maximum Amplitude was obtained in the four channels or at least 60 minutes have elapsed.

The percentage of platelet inhibition is calculated by the software of the manufacturer (Haemonetics®) using the following equation:[18]

$$= 100 - \frac{\text{Maximum Amplitude, channel 3} - \text{Maximum Amplitude, channel 2}}{\text{Maximum Amplitude, channel 1} - \text{Maximum Amplitude, channel 2}} \times 100$$

According to the previous published literature, we classified a patient as aspirin resistant by TEGPM if the percentage of platelet inhibition in the arachidonic acid pathway was <50%[3] and clinical aspirin resistant to that patient taking aspirin at therapeutic dose, with echocardiographic evidence of thrombosis and/or signs and symptoms of thrombosis.

Echocardiogram

All of our study subjects had an echocardiogram performed within 1 week from obtaining TEGPM results. The echocardiogram was completed by a trained echocardiographic technician with a General Electric® Vivid E9 echocardiograph (GE Healthcare, Wauwatosa, Wisconsin, United States of America) and read by a board-certified/eligible paediatric cardiologist.

Statistical analysis

Numerical variables without a normal distribution were analysed with a Mann–Whitney U test. χ^2 test was used for categorical variables. Pearson's correlation was used for continuous numerical variables. Multiple logistic regression analysis was done for all variables as a final analysis. We considered results to be statistically significant if they had a p value of <0.05 with a 95% confidence interval.

Results

Our study population consisted of 25 subjects, 11 female patients, with a mean age of 10.7 ± 8.9 years, and 14 male patients, with a mean age of 9.4 ± 4.4 years. Details of subjects and type of surgeries are given in Table 1. Aspirin resistance by thromboelastrogram plus platelet mapping was found in 72% of all patients (18/25).

There was no correlation between the dose of aspirin calculated by mg/kg and the levels of platelet inhibition by arachidonic acid (confidence interval (CI) 95%, p: 0.7) (Fig 1). Of note, 72% (18/25) of our study subjects were taking the maximum dose of aspirin at 81 mg every day. The average dose for all subjects was 2.9 mg/kg/dose.

When sorted by type of surgery, 73% (14/19) of post-Fontan patients presented with aspirin resistance, whereas the rest of our study population was identified to have 67% (4/6) as may be seen in Table 2. When grouped by underlying diagnosis, 70% (20/25) of our study population had a cyanotic heart lesion as their underlying disease (Table 3). Patients with diagnosis of

Table 1. Subjects divided by gender and surgical procedure.

Surgery/age	Male	Female	Total
Age	9.4 ± 4.4 years	10.7 ± 8.9 years	9.9 ± 6.26 years
Fontan surgery	12	7	19
Cavopulmonary anastomosis	1	2	3
Hybrid procedure	1	0	1
Coronary by-pass	0	1	1
Coronary aneurysm	0	1	1

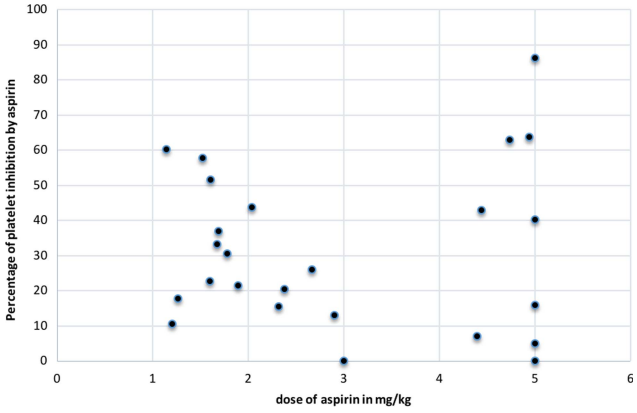

Figure 1. Correlation between dose of aspirin per mg/kg and percentage of platelet inhibition by aspirin (p: 0.7 CI: 95%).

https://doi.org/10.1017/S1047951118000021 Published online by Cambridge University Press

Table 2. Subjects divided by response to platelet inhibition and surgical procedure.

Type of correction	Total	Sensitive	Resistant	Percentage of non-responsiveness
Fontan	19	5	14	73
Cavopulmonary anastomosis	3	2	1	33
Coronary by-pass/ coronary aneurysm	2	0	2	100
Hybrid surgery	1	0	1	100

Table 3. Subjects divided by cardiac congenital disease and response to platelet inhibition.

Diagnosis	Total	Sensitive	Resistant	Percentage of non-responsiveness
HLHS*	5	0	5	100
DORV*	2	1	1	50
DILV*	4	1	3	75
Tricuspid atresia*	6	3	3	50
D-TGA*	2	0	2	100
TAPVR*	1	1	0	0
AV-canal	3	1	2	67
Coronary anomalies	2	0	2	100

AV-canal = common atrioventricular canal; DILV = double-inlet left ventricle; DORV = double-outlet right ventricle; D-TGA = dextro-trasposition of the great arteries; HLHS = hypoplastic left heart syndrome; TAPVR = total anomalous pulmonary venous return
*Cyanotic lesion

double-outlet right ventricle and tricuspid atresia had the least amount of aspirin resistance (Table 3, Fig 2). The average time in our population from surgery to the performance of the test TEGPM was 5.3 years.

Patients were divided into two groups: sensitive and resistant to aspirin by TEGPM. When compared for possible confounding factors, we found no statistical difference between both groups when assessed for variables of haemoglobin, haematocrit, platelet level, age, weight, height, and body mass index by Mann–Whitney test (Table 4).

There were eight female patients who were resistant by the test to aspirin – 72% of female patients – and 10 male patients with aspirin resistance by the test – 71% of male patients. Differences between gender were not statistically significant by χ^2 test (score: 0.3645: CI 95%, $p \geqslant 0.5$).

In one patient with tricuspid atresia and extra-cardiac fenestrated Fontan, an intra-systemic thrombus was identified at the level of the Fontan baffle, not obstructing the flow. The level of platelet inhibition in this patient was 64%. The time since the surgery and the detection of the thrombus was 7 months and 17 days.

Discussion

Thromboembolic complications in the postoperative period in patients with a single-ventricle physiology are an area of great concern. The aetiology for this increased thrombogenecity is incompletely understood.[19] In addition, this complication appears to occur at any time of the life span of these patients. The prevalence of thromboembolic events after a Fontan surgery has been described to be 8.1% after a mean follow-up of 8.4 years.[19] Aspirin is the most common medication used in the United States of America hospitals to prevent thrombosis in this specific population, but its efficacy has never been tested in a randomised clinical trial.[20] Aspirin is also an equivalent treatment compared with warfarin in children after Fontan surgery.[21] There is now an open debate on the concept of aspirin resistance in the paediatric population, although there has not been any laboratory test that has been able to clearly define it. Variability between laboratory test makes this task more challenging.[9]

In our study, aspirin resistance by TEGPM is high (72%). These results are similar to those previously published by Mir et al, who evaluated aspirin resistance with TEGPM in the immediate postoperative period of cyanotic lesions in 1-month-old patients taking aspirin at therapeutic dose. They reported a level of aspirin resistance of 80%.[3] This may be explained by an increased activation of platelets after a vascular surgery.[22] Furthermore, it has been demonstrated that patients less than 1 month have a variable response to aspirin.[23] It is important to note that Mir et al were able to correlate the results of aspirin resistance by TEGPM and high levels of urinary 11-dehydroxy-thromboxane B2, which is a test that has been able to predict cardiovascular events in the adult population.[24] Similarly, our results parallel those described by Saini et al as well, who reported a level of aspirin resistance by TEGPM of 75% on patients on extracorporeal membrane oxygenation.[25] Our results suggest that this high aspirin resistance by the test might be maintained a longer period of time after surgery and perhaps is independent of the use of extracorporeal membrane oxygenation as the levels of aspirin inhibition are similar in our study population. Further, bigger cohorts are needed to clearly define whether the similarity encountered by TEGPM in such diverse environments is due to intrinsic factors in the platelet function or it is because of the test itself.

We were not able to establish a correlation between aspirin resistance by platelet mapping and clinical thrombosis. In fact, the only patient with a thrombus identified was classified as aspirin sensitive. At this point, it is not clear whether the use of thromboelastogram and platelet mapping might have a relevant role for monitoring anti-thrombotic therapy in children with CHDs.

One of the possible factors affecting the results of thromboelastogram plus platelet mapping is the use of heparin in the sample to measure maximum amplitude in the arachidonic acid sample (Channel 3). Nelles et al has reported this effect. They demonstrated that platelets in heparinised samples had an increase in procoagulant platelet microvesicles and this might be responsible for up to 29–58% increase in the value of maximum amplitude in the arachidonic acid sample.[26]

It is the opinion of the authors that a possible next step in the development of TEGPM test might be replacing heparin by salicylate – the active metabolite of aspirin – in a known therapeutic concentration in the arachidonic acid channel. This creates an in vitro test that could potentially predict the effectiveness of aspirin in a patient before starting therapy. At the same time, it eliminates the activation of platelets by heparin and overcomes the problem of monitoring the effectiveness of anti-thrombotic

https://doi.org/10.1017/S1047951118000021 Published online by Cambridge University Press

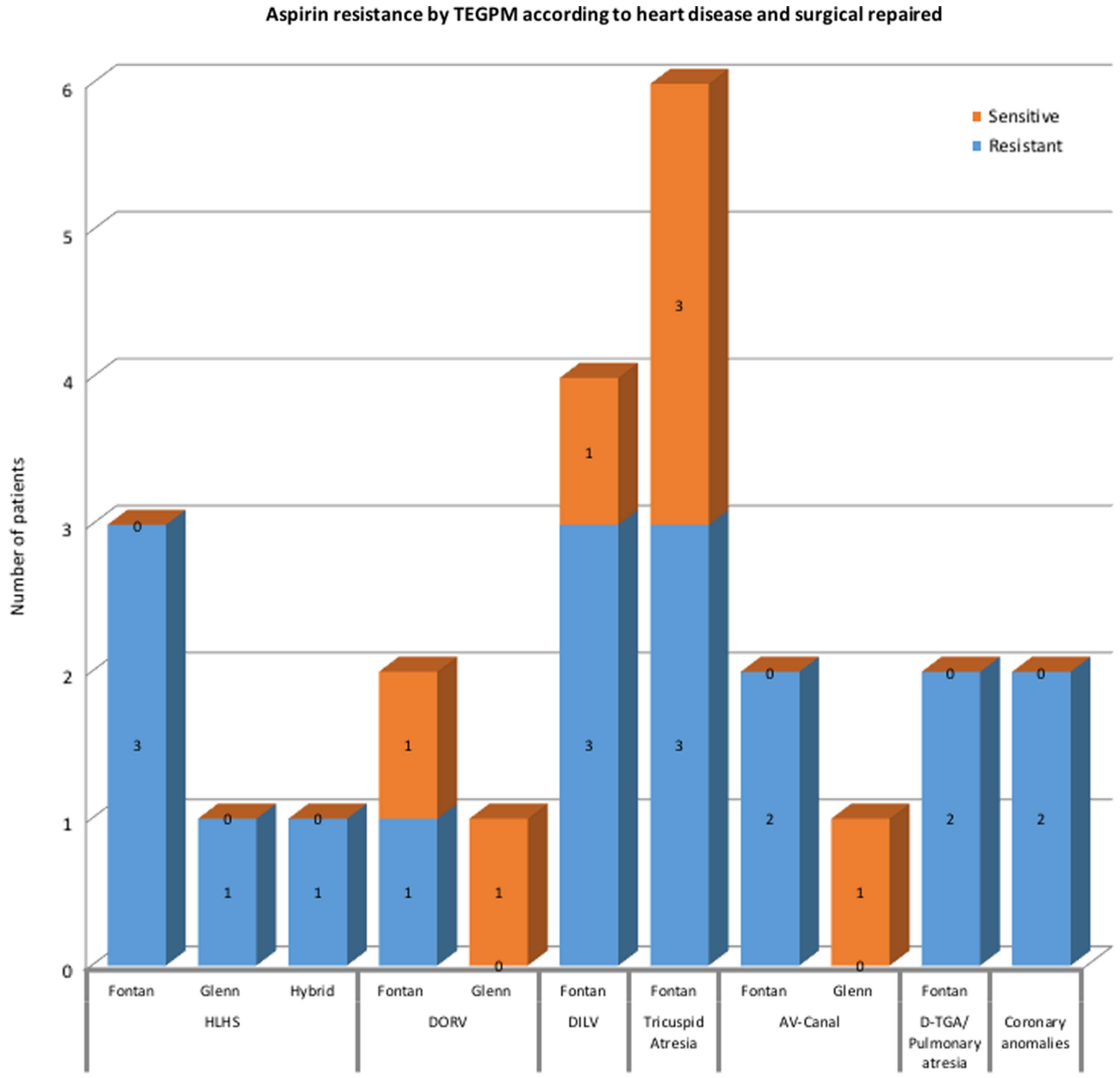

Figure 2. Aspirin resistance by TEGPM according to heart disease and surgical repair. AV = atrioventricular; DILV = double-inlet left ventricle; DORV = double-outlet right ventricle; D-TGA = dextro-trasposition of the great arteries; HLHS = hypoplastic left heart syndrome.

therapy in a non-compliant patient. On the other hand, this step might be able to identify a patient who is genetically predisposed not to respond to aspirin, opening the door for a future individualised anti-thrombotic therapy.

In the two previous studies and the present, the given definition of aspirin resistance was arbitrarily defined as a level of inhibition in response to arachidonic acid of <50% by TEGPM. We believe that this definition needs to be revised in light of our findings of one patient with a thrombus at level of the fenestration of the Fontan and a level of inhibition of 63%. These authors suggest lowering the definition to 20%, which is the average that we encountered in our patients with aspirin resistance (Table 4). Furthermore, owing to the complexity of factors that can alter platelet activation, we believe that it is reasonable to classify a patient between 20 and 50% level of inhibition as hypo-responsive or high on-aspirin treatment platelet reactivity. A correlation between the levels of platelet inhibition when assessing aspirin therapy by thromboelastogram plus platelet mapping and clinical outcomes is needed to make this classification operational.

The majority of our subjects had a cyanotic lesion as their underlying initial diseases (70%, n = 20, Table 4). This high incidence of aspirin resistance is also in accordance with the result presented by Heistein et al, who demonstrated that the cyanotic lesions are more likely to present aspirin resistance (39.5%).[1] However, Heistein et al used Platelet Function Analyzer–100. This test is not equivalent to TEGPM

Thromboelastometry has been previously used by Lison et al[27] in the post-surgical period to evaluate the haemostasis of adult patients after a major surgery, demonstrating an increase in the clog firmness up to the day 6 after surgery. We believe that a possible haematological derangements after a vascular surgery

https://doi.org/10.1017/S1047951118000021 Published online by Cambridge University Press

Table 4. Subjects demographics.

Variables	Resistant	Sensitive	p
N	18	7	
Percentage of inhibition	20.19 ± 13.47% (n: 18)	62.47 ± 11.38% (n: 7)	0.0001***
Female/male	8\10	3\4	0.54
Age	10.65 ± 6.92 years (n: 18)	8.07 ± 4.71 years (n: 7)	0.54
BMI	47.25 ± 26.11 kg/m^2 (n: 16)*	62.55 ± 35.82 kg/m^2 (n: 7)	0.28
Weight	34.83 ± 17.68 kg (n: 18)	33.68 ± 23.94 kg (n: 7)	0.88
Height	128.26 ± 30.21 cm (n: 18)	126.91 ± 34.34 cm (n: 7)	0.83
Platelets	241,000 ± 121,000 (n: 16)**	234,000 ± 66,000 (n: 7)	0.89
Hgb	15.39 ± 1.45 mg/dl (n: 16)**	14.79 ± 1.50 mg/dl (n: 7)	0.4
Hct	46.38 ± 6.90 (n: 16)**	44.01 ± 3.67 (n: 7)	0.67

BMI = body mass index; Hct = haematocrit; Hgb = haemoglobin
*Two patients were excluded because they were >18 years
**Two patients did not have a complete blood count within 2 weeks of the TE
***Statistically significant results

may predispose these patients to be more prone to not respond to the anti-platelet treatment.

Although our results are laboratory findings and do not correlate with clinical thrombosis, nor are evidence of haemostasis pathology, these haematological derangements are commonly identified after cardiovascular surgeries in CHDs.[28] For example, there has been noted an increase in the levels of Factor VIII zand Von Willebrand factor after a vascular surgery.[21] The relation of this increase and the prothrombotic state after surgery is still not clear.[21]

Particularly in CHD surgeries, adult-survivor patients post-Fontan have been shown to have a 23% increase in the Von Willebrand factor levels, as well as P-selectin, in the platelet's surface.[29] This increased activation on P-selectin in platelets has also been found in healthy children when compared with healthy adults,[30] pointing to a multi-factorial cause that combines specific characteristics of a developing haemostatic system in children and the physiology after a vascular surgery that might predispose to clinical aspirin resistance. It is well described that Von Willenbrand factor acts as a chaperone for factor VIII , which has its reservoir in the Weibel–Palade bodies on the endothelium,[31] whose integrity in any case might be compromised because of chronic cyanosis and/or surgery.

In our study, no correlation with age in months and level of platelet inhibition was observed. There is a weak positive trend between body mass index and platelet inhibition when the outliers of our sample are excluded – two patients >18 years of age. We consider that a bigger sample might show statistical significance (Figs 3 and 4).

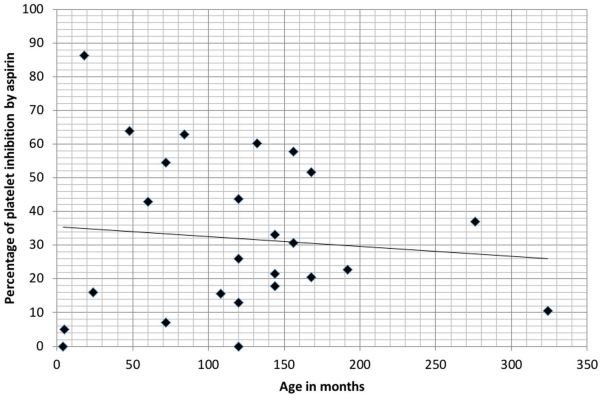

Figure 3. Correlation between age in months and level of platelet inhibition by aspirin R -0.0971 (CI 95%, p: 0.64).

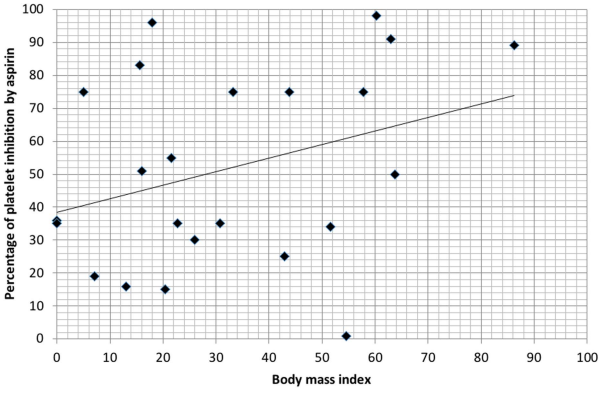

Figure 4. Correlation between body mass index and level of platelet inhibition: 0.3309 (CI: 95%, p: 0.107).

Conclusions

Aspirin resistance in children with congenital heart conditions after surgical repair, defined as a percentage of inhibition <50% by TEGPM, is high.

Our study demonstrates aspirin resistance as a laboratory finding. Correlation with clinical resistance – that is, a patient taking aspirin that presents with thrombosis – is still required. A standard definition of aspirin resistance as a first step and validation of this definition on large prospective studies is needed.

The accuracy of the TEGPM to predict clinical disease (thrombosis) is in question, given the published data that sets the standard for aspirin resistance. However, our patient numbers are

https://doi.org/10.1017/S1047951118000021 Published online by Cambridge University Press

not high enough to reach a conclusion on this. Further research is needed to assess the appropriate therapy for anti-coagulation/anti-platelet therapy on patients with CHD.

In the current era of stenting, implantable valves, and interventions in the vascular space, a more proactive approach to monitor anti-thrombotic therapy is needed, rather than waiting for morbid events to define outcomes.

Acknowledgements. The authors would like to thank all Driscoll Children's Hospital staff who took care of our patients. The authors are also thankful to Paige Cooper RN BNS and Christianna Donald RN BNS for their help on the chart's search, as well as Jose H. Guardiola PhD Assistant professor at Texas A&M Department of Mathematics and Statistics for the statistical analysis and Teddy Sefawn MSC Laboratory Driscoll Children's Hospital.

Financial Support. None.

Conflicts of Interest. None.

References

1. Lisa CH, Scott WA, Zellers TM, et al. Aspirin resistance in children with heart disease at risk for thromboembolism: prevalence and possible mechanisms. Pediatr Cardiol 2008; 29: 285–291.
2. Yee DL, Dinu BR, Sun CW, et al. Low prevalence and assay discordance of "aspirin resistance" in children. Pediatr Blood Cancer 2008; 51: 86–89.
3. Mir A, Frank S, Journeycake J, et al. Aspirin resistance in single-ventricle physiology: aspirin prophylaxis is not adequate to inhibit platelets in the immediate postoperative period. Ann Thorac Surg 2015; 99: 2158–2164.
4. Adatia MRCP, Barrow SE, Stratton PD, Miall-Allen VM, Ritter JM, Haworth SG. Thromoboxane A2 and prostacyclin biosynthesis in children and adolescents with pulmonary vascular disease. Circulation 1993; 88: 2117–2122.
5. Lordkipanidzé M, Pharand C, Schampaert E, Turgeon J, Palisaitis DA, Diodati JG. A comparison of six major platelet function tests to determine the prevalence of aspirin resistance in patients with stable coronary artery disease. Eur Heart J 2010; 28: 1702–1708.
6. Cattaneo M. The clinical relevance of response variability to antiplatelet therapy. Hematology Am Soc Hematol Educ Program 2011; 2011: 70–75.
7. Gasparyan AY, Watson T, Lip GY. The role of aspirin in cardiovascular prevention: implications of aspirin resistance. J Am Col Cardiol 2008; 51: 1829–1843.
8. Eikelboom JW, Hankey GJ, Thom J, et al. Incomplete inhibition of thromboxane biosynthesis by acetylsalicylic acid; determinants and effect on cardiovascular risk. Circulation 2008; 118: 1705–1712.
9. Schmugge M, Speer O, Kroiss S, et al. Monitoring aspirin therapy in children after interventional cardiac catheterization: laboratory measures, dose response, and clinical outcome. Eur J Pediatr 2015; 174: 933–941.
10. Tran HA, Anand SS, Hankey GJ, Eikelboom JW. Aspirin resistance. Thromb Res 2007; 120: 337–346.
11. Emani S, Trainor B, Zurakowski D, Bair C, Fynn-Thompson F, Pigula FA, Emani A. Aspirin unresponsiveness predicts thrombosis in high-risk pediatric patients after cardiac surgery. J Thorac Cardiovasc Surg 2014; 148: 810–814; discussion 814–16.
12. Long E, Pitfield AF, Kissoon N. Anticoagulation therapy; indications, monitoring and complication. Pediatr Emerg Care 2011; 27: 55–61; quiz 62–64.
13. Monagle P, Chan AK, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physician Evidence-Based Clinical Practice Guidelines. Arch Dis Child 2004; 89: 1168–1173.
14. Thon KE, Hanslik A, Male C. Anticoagulation in children undergoing cardiac surgery. Semin Thromb Hemost 2011; 37: 826–833.
15. Nalyaka S, Radhakrishnan A, Englyst N, Weir N, Curzen N. Aspirin resistance in ischemic stroke: insights using short thrombelastography. J Stroke Cerebrovasc Dis 2013; 22: 1412–1419.
16. Kroll M. Thromboelastography: theory and practice in measuring hemostasis. Clin Lab News 2010; 36: 8–10.
17. Swallow RA, Agarwala RA, Dawkins KD, et al. Thromboelastography: potential bedside tool to assess the effects of antiplatelet therapy? Platelets 2006; 17: 385–392.
18. Hobson AR, Petley GW, Dawkins KD, Curzen N. A novel fifteen minute test for the assessment of individual time-dependent clotting response to aspirin and clopidogrel using modified thromboelastography. Platelets 2007; 18: 497–505.
19. Idorn L, Jensen AS, Juul K, Reimers JI, et al. Thromboembolic complications in Fontan patients: population-based prevalence and exploration of the etiology. Pediatr Cardiol 2013; 34: 262–272.
20. Wessel DL, Berger F, Li JS, et al. Clopidogrel in infants with systemic-to-pulmonary-artery shunts. N Engl J Med 2013; 368: 2377–2384.
21. Iyengar AJ, Winlaw DS, Galati JC, et al. No difference between aspirin and warfarin after extracardiac Fontan in a propensity score analysis of 475 patients. Eur J Cardiothorac Surg 2016; 50: 980–987.
22. Schneider GS, Rockman CB, Berger JS. Platelet activation increases in patients undergoing vascular surgery. Thromb Res 2014; 134: 925–926.
23. Romlin BS, Wahlander H, Stromvall-Larsson E, Synnergen M, Baghaei F, Jeppson A. Monitoring of acetyl salicylic acid-induced platelet inhibition with impedance aggregometry in children with systemic-to-pulmonary shunts. Cardiol Young 2013; 23: 225–232.
24. Szczeklik W, Stodolkiewicz E, Rzeszutko M, Tomala M, Chrustowicz Am Zmudka K, Sanak M. Urinary 11-dehydro-thromboxane B2 as a predictor of acute myocardial infarction outcomes: results of Leukotrienes and Thromboxane in Myocardial Infarction (LTIMI) study. J Am Heart Assoc 2016; 5: e003702.
25. Saini A, Hartman ME, Gage BF, et al. Incidence of platelet dysfunction by thromboelastography-platelet mapping in children supported with ECMO: a pilot retrospective study. Front Pediatr 2016; 3: 1–8.
26. Nelles NJ, Chandler WL. Platelet mapping assay interference due to platelet activation in heparinized samples. Am J Clin Pathol 2014; 142: 331–338.
27. Lison S, Weiss G, Spannagl M, Heindl B. Postoperative changes in procoagulant factors after major surgery. Blood Coagul Fibrinolysis 2011; 22: 190–196.
28. Odendard KC, McGowan FX, Zurakowski D, et al. Procoagulant and anticoagulant factor abnormalities following the Fontan procedure: increased factor VIII may predispose to thrombosis. J Thorac Cardiovasc Surg 2003; 125: 1260–1267.
29. Tomkiewicz-Pajak L, Hoffman P, Trojnarska O, Lipcznska M, Podolec P, Undas A. Abnormalities in blood coagulation, fibrinolysis, and platelet activation in adult patients after the Fontan procedure. J Thorac Cardiovasc Surg 2014; 147: 1284–1289.
30. Yip C, Linden M, Attard C, Monagle P, Ignjatovic V. Platelets from children are hyper-responsive to activation by thrombin receptor activator peptide and adenosine diphosphate compared to platelets from adults. Br J Hematol 2015; 168: 526–532.
31. Wagener DD, Olmsted JB, Marder VJ. Immunolocalization of von Willebrand protein in Weibel-Palade bodies of human endothelial cells. J Cell Biol 1982; 95: 355–360.

https://doi.org/10.1017/S1047951118000021 Published online by Cambridge University Press