May 11th, 11:30 AM - 1:30 PM

# Bivalirudin and Thrombolytic Therapy: A Novel Successful Treatment of Severe Aortic Arch Thrombosis in a Term Neonate

Amjad Taha

# Research Abstract Title

**Submitting/Presenting Author (must be a trainee): Amjad Taha MD, FAAP**
**Primary Email Address: ataha@cmh.edu**

☐ Medical Student
☐ **Resident/Psychology Intern (≤ 1 month of dedicated research time)**
☐ Resident/Ph.D/post graduate (> 1 month of dedicated research time)
**X Fellow**

**Primary Mentor (one name only): Mahdi Alsaleem MD**
**Other authors/contributors involved in project: Ayan Rajgarhia MD**

**IRB Number: N/A**

**Describe role of Submitting/Presenting Trainee in this project (limit 150 words):**
**Amjad Taha is the primary author who has the most contribution to the work in terms of direct patient care, patient's parents contact and wrote most of the report.**

## TITLE OF CASE

Bivalirudin and Thrombolytic Therapy: A Novel Successful Treatment of Severe Aortic Arch Thrombosis in a Term Neonate

## SUMMARY

An early term infant with uncomplicated perinatal history was found to have a large thrombus in the aortic arch after he failed regular newborn critical congenital heart defect (CCHD) screen. He responded well to Bivalirudin thrombolytic and tissue-Plasminogen activator (tPA) combination therapy, with a significant resolution of the thrombus. The infant tolerated hospital admission well with no significant complications. He was discharged home on daily aspirin at two weeks of life. To our knowledge, the combination therapy approach with Bivalirudin and tPA is the first one reported in the literature in the neonatal age group.

## BACKGROUND

Aortic arch thrombosis can be a rare, life-threatening condition in neonates. Presentation varies between affected neonates based on the clot's size and location, degree of occlusion, and embolic potential to other vital organs. Given the limited reported cases in the literature, a standardized treatment approach is not available. Multiple options of management have been reported to prevent the high risk of mortality and morbidity. We present an early-term neonate who had a large clot occluding the aortic arch. The infant

presented to our unit after he failed the standard congenital heart newborn screen. After multidisciplinary team evaluation and parenteral counseling, he was treated successfully with combination therapy of Bivalirudin and tPA.

## CASE PRESENTATION

A two-day-old male infant was born at 37 weeks of gestation by normal vaginal delivery after an uncomplicated pregnancy. Apgar scores were 8 and 9, at 1 and 5 minutes, respectively. The birth weight was 3 kg. His postnatal course was uncomplicated until he failed his critical congenital heart defect screen (CCHD). His pre-ductal oxygen saturation (SpO2) was 100% compared to a post-ductal SpO2 of 88-90%. This concerning finding prompted further evaluation by echocardiogram, which was concerning for what appeared at that point to be severe aortic coarctation and possible interrupted aortic arch associated with decreased left ventricular function. The infant was then transferred to our tertiary center for further evaluation. At admission, he was hemodynamically stable with stable vital signs (Temperature; 36.8$^{o}$, heart rate of 153 beats per minute, respiratory rate of 60 breaths per minute, systolic blood pressure obtained by cuff was 76 mmHg and 59 mmHg obtained from the right arm and right leg, respectively with diastolic of 47 mmHg and 30 in the same order). Weight on admission was 2.8 kg, with no apparent signs of dehydration. Cardiovascular examination showed regular heart rate and normal rhythm, quiet precordium, normal first and second heart sounds, no murmurs, pulses were regular in all extremities, and capillary refill was less than 3 seconds. The rest of the physical examination was unremarkable.

A repeat echocardiogram obtained on admission (day two of life) to our center revealed a large ovoid echogenic structure within the aortic arch just distal to the left subclavian artery and proximal to the ductal ampulla, figure 1. This appearance was more indicative of aortic thrombus rather than coarctation. The mass measured about 7 mm x 3.5 mm and caused an obstruction of the aortic blood flow. Large non-restrictive patent ductus arteriosus and moderate left ventricular dysfunction suggested by an ejection fraction of 40.2% (Z score of -4.3). Computed tomography (CT) of the chest with angiography was performed on the same day to have a clearer anatomical understanding of the location and the extent of the thrombus. It did show near-complete occlusion of the aortic arch and the descending aorta just distal to the origin of the left subclavian artery with large PDA providing most of the blood flow in the descending aorta, figure 2. It did also reveal cardiomegaly and mild evidence of hepatomegaly.

## INVESTIGATIONS

As the etiology of the aortic obstruction felt to be more likely related to the presence of significantly large size thrombus; Hematology service was consulted. Further history revealed no family history of thrombosis or bleeding disorder. Initial complete blood count showed a low Hemoglobin of 11.8 g/dL (most likely due to multiple blood sample draws) and a platelet count of 227 x$10^{3}$/mcL. Bassline coagulation testing for prothrombin (PT) and partial prothrombin (PTT) times, fibrinogen was within normal limits for age and gestational age. Thrombosis panel testing for the common mutations associated with thrombophilia (Factor V Leiden variant c.1601 G>1, Factor II (prothrombin gene) variant

c.*97G>A, ADAMTS13, FGA, FGB, FGG, HRG, PROC, PROS1, SERPINC1, THBD) were negative. A chromosomal microarray test showed a typical XY chromosomal pattern and no detected abnormalities. Association with the antiphospholipid syndrome was ruled out by negative serological testing for; phospholipids IgM and IgG antibodies for both the mother and the baby.

## DIFFERENTIAL DIAGNOSIS

Given the infant's clinical presentation, the diagnosis of aortic arch obstruction was made and was initially thought to be related to cardiac malformations such as coarctation of the aorta, interrupted aortic arch, and hypoplastic left heart syndrome. Common symptoms and signs associated with this obstruction were not evident on admission, and the infant appeared in stable condition. The blood flow to the organs was well maintained by the flow directed through the large PDA and bypassing the obstructed segment of the aorta.
After further evaluation by a repeat echocardiogram and CT angiogram, a large, nearly occlusive aortic thrombus was likely the infant condition's etiology. The differential diagnosis for the etiology of the large thrombus seen in our case included prothrombotic disorders listed in table 1.

Table 1: Prothrombotic conditions associated with increased risk of neonatal thrombosis

| Conditions that can result in thrombosis |
|---|
| Protein C or S deficiencies |
| Antiphospholipid antibodies (including anticardiolipin antibodies, lupus anticoagulant) |
| Heparin cofactor II deficiency |
| Dysfibrinogenemia |
| Prothrombin G20210A gene mutation |
| PAI-1 4G/5G gene mutation |
| Factor V Leiden mutation |
| MTHFR C677T gene mutation |
| Prothrombin G20210A gene mutation |
| Antiphospholipid antibodies |
| Inherited thrombophilia |
| Congenital heart disease and pulmonary hypertension |

| |
|---|
| Congenital nephrotic syndrome |
| Dehydration |
| Sepsis |
| Surgical procedures or Extracorporeal membrane oxygenation |

Table 1: List of conditions associated with neonatal thrombosis. MTHFR: Methylenetetrahydrofolate reductase. PAI: Plasminogen activator inhibitor.

## TREATMENT

On admission, prostaglandin E infusion ( 0.03 mcg/kg/min) was started to keep the PDA patency and maintain hemodynamic stability. The infusion was discontinued on day 4 of life. After clinical evaluation and based on the echocardiogram findings and the CT angiography of the chest, consultations with cardiology, cardiovascular surgery, and hematology services were pursued. To prevent and control the thrombosis progression, bivalirudin infusion was started on day 2 of life at 0.2 mg/kg/hr ( dilution was made by mixing 50 mg of bivalirudin in 10 ml of normal saline) and titrated to achieve a heparinized PTT goal of 60-90 seconds. Given the critical size and location and to further help dissolve the thrombus, thrombolytic therapy with tissue plasminogen activator (tPA) was given ( 0.3 mg/kg/hr, infused over 6 hours) on day four of life. A cranial ultrasound obtained prior to tPA therapy showed no intracranial bleeding. The timeline of medication administration and the corresponding heparinized PTT values are shown in table 2.

Table 2

| Day of life | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| Bivalirudin dose (mg/kg/hr) | | 0.2 | 0.2 | 0.1 | 0.2 | 0.2 | discontinued |
| tPA (mg/kg/hr) | | | | 0.3 mg/kg/hr for 3 hours | | | |
| hPTT ( seconds) | 37.1 | 66.8 | 62.0 | 71.9 | 59 | 70 | 59.6 |

Table 2: The medication timeline with the corresponding coagulation profile. tPA; tissue plasminogen activator, PT; prothrombin time, hPTT: heparinized partial thrombin time.

## OUTCOME AND FOLLOW-UP

The infant developed scalp hematoma at a previous peripheral intravenous catheter (PIV) site on the right temporal region. A head ultrasound was concerning for subgaleal hematoma, which prompted discontinuation of tPA 30 minutes before finishing 6 hours of planned treatment duration. The size of the hematoma significantly reduced shortly after stopping tPA and subsequently disappeared after 24 hours. Repeated echocardiogram obtained 24 hours after tPA infusion showed a significant reduction in the size of the thrombus (4mm x 3mm) and a substantial decrease in the obstruction to flow in the descending aorta, figure 3. Given the considerable response to tPA, surgical intervention was not needed. Follow up echocardiogram obtained 72 hours showed near-complete resolution of the thrombus, figure 4. The decision was made to discontinue the Bivalirudin infusion and to start Aspirin 20 mg daily given orally for a planned total duration of 6 weeks. The infant was then discharged home in stable condition at two weeks of age.

## DISCUSSION

Extensive aortic arch neonatal thrombosis is a rare condition. Only 20 cases have been reported in the literature.[1] The exact etiology of this entity is unknown. The majority of neonatal patients have a clinical presentation mimicking aortic coarctation. This similarity is derived from the same primary pathophysiological mechanism, which is aortic arch partial or complete occlusion. Neonatal aortic arch thrombosis has a significant mortality rate, as almost more than half of neonates diagnosed died in the postnatal period.[1] Etiology is mostly unknown; however, some reports associated this entity with sepsis, congenital cytomegalovirus (CMV) infection, family history of thrombosis, polycythemia, or lupus anticoagulant. [2-5]

Given the high morbidity and mortality associated with this condition, early recognition and treatment are essential. Echocardiograms are usually indicative of the diagnosis. However, further imaging with CT angiography and/or chest Magnetic resonance imaging (MRI) is recommended to evaluate the extent of the involvement and the associated cardiac and non-cardiac anomalies.

Treatment approaches vary between centers. Multidisciplinary team evaluation, including cardiology, cardiovascular surgery, radiology, and hematology, is recommended to evaluate the anatomical involvement, options for medical therapy, and surgical intervention feasibility. Anticoagulation with intravenous or low molecular weight heparin has been trialed in previous cases with variable success.[6] Thrombolytic therapy using tissue plasminogen activator has also been attempted. However, the results were inconclusive. [1]

The surgical approach, either directly or using a transcatheter approach, was performed in previous cases. Surgical intervention may be considered in those who fail to respond to medical therapy or those where medical therapy is contradicted due to high bleeding risk.

In our case, due to the large extent of the thrombus and the absence of alarming signs for coagulation problems, treatment with a thrombolytic agent was attempted. Bivalirudin is a relatively recent anticoagulant treatment modality that has been recently shown to be safe and effective in children and infants in comparison to heparin.[7] It works as a direct thrombin inhibitor that was approved by the food and drug administration (FDA) in 2000 for use in adults.[8] Although not FDA approved for children and neonates, clinicians have found a potential advantage of using Bivalirudin in children, especially in those who are heparin unresponsive, resistant, or suffered from a significant side effect due to heparin use. [9] Possible explanation of the benefit of Bivalirudin over heparin in the neonatal population could be from

the different mechanisms of action, as heparin acts mainly by potentiating the effects of the endogenous antithrombin, figure 5. On the other hand, Bivalirudin is a direct thrombin inhibitor that does not require antithrombin for it's anticoagulation effect, and has a some fibrinolytic effect. In addition, Antithrombin level is physiologically low and it's concentration changes rapidly in the first 6 months of life, making the adequate control of heparin and achieving a therapeutic level more difficult than with Bivalirudin. In addition, Bivalirudin binds to both plasma and bound thrombin as opposed to heparin, which only works on inhibiting plasma thrombin.[10]

Tissue plasminogen activator has been suggested in previous studies to provide an effective method for thrombus dissolution in neonates. [11] Close follow-up and continuous monitoring are highly recommended when using tPA. In our case, tPA infusion was stopped as the patient developed concerning scalp hematoma after 3 hours into the infusion period.

Aspirin was used in our case given the arterial nature of the thrombus in our case, and due to the antiplatelet effect to to allow for healing and to prevent further arterial thrombosis.

To our knowledge, this is the first reported use of Bivalirudin and tPA combination in neonatal aortic arch thrombosis. Regling et al. have reported a successful combination management approach in a pediatric patient with near occlusive organ threatening thrombus. [12]

## LEARNING POINTS/TAKE HOME MESSAGES

-Neonatal aortic arch thrombosis is a rare condition that affects neonates. The clinical presentation is very similar to aortic coarctation

-Bivalirudin and thrombolytic therapy represent a successful management approach for neonates with large aortic arch thrombosis.

## REFERENCES


1. Knadler JJ, Zobeck M, Masand P, Sartain S, Kyle WB. In Utero Aortic Arch Thrombosis Masquerading as Interrupted Aortic Arch: A Case Report and Review of the Literature. Pediatric cardiology. 2019;40(3):658-63.

2. Wieland I, Jack T, Seidemann K, Boehne M, Schmidt F, Happel CM, et al. Neonatal aortic arch thrombosis: analysis of thrombophilic risk factors and prognosis. Cardiology in the Young. 2014;24(1).

3. Lanari M, Lazzarotto T, Papa I, Venturi V, Bronzetti G, Guerra B, et al. Neonatal aortic arch thrombosis as a result of congenital cytomegalovirus infection. Pediatrics. 2001;108(6):e114-e.

4. Sheridan-Pereira M, Porreco RP, Hays T, Burke MS. Neonatal aortic thrombosis associated with the lupus anticoagulant. Obstetrics and gynecology. 1988;71(6 Pt 2):1016-8.

5. Metsvaht T, Hermlin T, Kern H, Kahre T, Starkopf J. Aortic arch thrombosis in a neonate with heterozygous carrier status of factor V Leiden mutation. Congenital heart disease. 2006;1(1-2):40-5.

6. Sharathkumar AA, LaMear N, Pipe S, Parikh S, Russell M, Simon A, et al. Management of neonatal aortic arch thrombosis with low-molecular weight heparin: a case series. Journal of pediatric hematology/oncology. 2009;31(7):516-21.

7. Young G, Tarantino M, Wohrley J, Weber L, Belvedere M, Nugent D. Pilot dose-finding and safety study of bivalirudin in infants< 6 months of age with thrombosis. Journal of Thrombosis and Haemostasis. 2007;5(8):1654-9.

8. Malloy KM, McCabe TA, Kuhn RJ. Bivalirudin use in an infant with persistent clotting on unfractionated heparin. The Journal of Pediatric Pharmacology and Therapeutics. 2011;16(2):108-12.
9. Barton R, Ignjatovic V, Monagle P. Anticoagulation during ECMO in neonatal and paediatric patients. Thrombosis Research. 2019;173:172-7.
10.Shammas NW. Bivalirudin: pharmacology and clinical applications. Cardiovascular drug reviews. 2005 Dec;23(4):345-60.
11. Hartmann J, Hussein A, Trowitzsch E, Becker J, Hennecke K. Treatment of neonatal thrombus formation with recombinant tissue plasminogen activator: six years experience and review of the literature. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2001;85(1):F18-F22.
12. Regling K, Callaghan MU, Rajpurkar M. Bivalirudin during thrombolysis with catheter-directed tPA in a heparin-refractory patient: A case report. Pediatric Blood & Cancer. 2020;67(2):e28094.

## FIGURES CAPTIONS

Figure 1: a. Echocardiogram image showing aortic arch with thrombus noted in the aortic isthmus (arrow). b. echocardiogram image with doppler flow showing blue flow going around the thrombus with near-complete obstruction (arrow) to the descending aortic flow.
Figure 2: CT angiography Axial (a) and coronal (b) sections; showing near-complete occlusion (arrows) of the aortic arch and the descending aorta
Figure 3: Repeated echocardiogram obtained 24 hours after tPA infusion showed a significant reduction in the size of the thrombus (4mm x 3mm).
Figure 4: Follow up echocardiogram obtained 72 hours showed complete resolution of the thrombus
Figure 5: A diagram showing the coagulation cascade and heparin, bivalirudin, and tPA sites of action, contributed by Mahdi Alsaleem MD.