RESEARCH ARTICLE

Anaemia in solitary acyanotic ventricular septal defect in comorbid with pneumonia or pulmonary hypertension: A retrospective study of 75 paediatric cases [version 1; peer review: 2 approved with reservations]

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Abstract

Background: Ventricular septal defects (VSD) are the second commonest congenital heart defects after bicuspid aortic valve. When left unrepaired, they can undergo spontaneous closure or elicit a spectrum of complications including pneumonia (PNA) or pulmonary hypertension (PH) with subsequent anaemia. In this retrospective study, we aim to establish and compare the prevalence of anaemia in patients with solitary acyanotic VSD in comorbid with PNA or PH.

Methods: A total of 75 case files of patients with solitary acyanotic VSD, who underwent surgical closure or device occlusion had haemoglobin level analysed prior to the procedure. The cohort included patients with (history of) PNA and PH, and asymptomatic. The cohort included 27 females and 48 males with mean age and weight of 8.3 ± 5.72 (3-24) months and 5.9 ± 3.9 (2.7-17.8) kilograms, respectively. Depending on associated complication and age, the cohort was divided: PNA (A), PH (B) and Control (C); and (I) young children ($\geq 3-6 \leq$) and (II) older children ($> 6- \leq 24$) months. We used 95 and 105 grams per litre as haemoglobin lower threshold level for (I) and (II), respectively.

Results: According to data analysis 27 patients (36%) in total had anaemia. Of the anaemia cohort 16 (59.3%) had PNA, 9 (33.3%) PH and 2 (7.4%) were asymptomatic. Of the cohort, 42 were young children, with anaemia prevalence of 19/42 (45.2%), while 24.2% of the older children had anaemia. Intergroup ANOVA independent sample t-test was significant ($p < 0.05$). In addition, intergroup *Tukey HSD* test for haemoglobin: A/B ($p > 0.05$), A/C ($p < 0.01$), B/C ($p < 0.01$).

Conclusion: Paediatric patients with acyanotic VSD in comorbid with PNA or PH are 8 and 4 times more susceptible to develop anaemia

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Approval Status ? ?

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version 2		
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2. **Raymond N. Haddad** , Saint Joseph University, Beirut, Lebanon

Any reports and responses or comments on the article can be found at the end of the article.

compared to asymptomatic counterparts. Susceptibility is even higher among young children (3-6months). However, a prospective study is needed to validate our findings.

Keywords

Ventricular septal defect, Pneumonia, Pulmonary hypertension, Anaemia

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Author roles: **Changwe GJ:** Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Zhang H:** Methodology, Resources; **Li H:** Formal Analysis, Supervision; **Farhaj Z:** Data Curation, Methodology; **Tewara MA:** Formal Analysis, Software; **Zhang W:** Validation, Visualization; **Zou C:** Funding Acquisition, Project Administration, Validation

Competing interests: No competing interests were disclosed.

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Introduction

Anaemia is a common complication of a myriad medical conditions often met in general ward. Its aetiology is complex and multifactorial, encompassing intrinsic and extrinsic factors¹⁻³. Cyanotic congenital heart defects are known to severely derail smooth blood flow with subsequent iron homeostasis dysregulation. Prevalence of anaemia amongst patients with cyanotic VSD is known and well documented in a variety of world literature². On the contrary, solitary acyanotic ventricular septal defect (VSD) exhibit a relatively smooth blood with unremarkable iron homeostasis dysregulation. However, depending on size and duration, solitary VSD can lead to pulmonary hyper-circulation with subsequent complications, including recurrent lower respiratory tract infection (pneumonia; PNA), pulmonary hypertension (PH), pulmonary vascular disease, heart failure and death^{4,5}.

PNA is known to cause local hypoxia with subsequent upregulation of erythropoiesis. In addition, certain causatives of PNA are known to compete for iron with the host, while others induce haemolysis, both leading to anaemia⁶. Equally, PH has been associated with severe forms of haemolytic anaemia in patients with haemoglobin disorder and erythrocyte membranopathies^{2,7}. In addition, free haemoglobin produced as a result of haemolysis depletes nitric oxide with subsequent vessel constriction, local hypoxia and exacerbation of PH^{8,9}. Both PNA and PH exhibit tendencies of inducing local hypoxia, leading to upregulation of erythrocyte synthesis. Adults and older children with enough iron store can tolerate such a condition without developing anaemia. However, infants and young children have inadequate iron stores. In addition, children below the age of 6-months fed exclusively on breast milk have limited source of iron replacement. For the reasons mentioned above, we hypothesize that paediatric patients with solitary acyanotic VSD coexisting with PNA or PH retain a risk of developing anaemia. In this retrospective study, we aim to establish the prevalence of anaemia in patients with solitary acyanotic VSD in comorbid with PNA or PH.

Methods

Case file details and classification

Between February 2014 and September 2018, 90 case files of patients with solitary acyanotic-VSD, who underwent either

surgical or minimal invasive closure in our Department of Cardiac Surgery, Shandong Provincial Hospital Affiliate of Shandong University were primarily selected for this study.

However, only 75 case files met study criteria, which included patients with a history of proven PNA by chest radiography with positive bacterial culture of trans-tracheal aspirate or polymerase chain reaction from nasopharyngeal swab. Pulmonary hypertension diagnosis was echocardiography based, except in 5 patients from PNA group, who presented in heart failure state. Excluded from this study were 15 files of patients: 7, sickle cell; 4, β -Thalassemia; 4, blood transfusion.

Among the 75 files were 48 males (75.64%) and 27 females with mean age and weight of 8.3 ± 5.7 (3–24) months and 3.8 ± 3.0 kilograms, respectively. Depending on the associated complication, the cohort was then divided into three groups: A, PNA (n=30); B, PH (n=25); and C, control (n=20). Based on age, the cohort was further split into two groups: I, young children (≥ 3 – ≤ 6); II, older children (> 6 – ≤ 24) months. The patient demographic and clinic characteristics (Table 1) and hematologic profile (Table 2) reflects pre-procedure state.

Data variables

Statistical analysis. Data was analysed using IBM SPSS-software (one-way-ANOVA) and all statistics expressed as mean $\pm$ standard deviation. Intergroup haemoglobin level was compared using independent samples student's t-test. Statistical comparison of proportions was analysed using *Tukey HSD Test*, and the probability value of less than 0.05 was considered significant. Patient proportions are expressed in number and percentage (n, %).

Results

In this study, the haemoglobin reference range for groups: I and II were (95–135g/L) and (105–135g/L) respectively. This thus, conforms with local protocol.

According to data analysis in Table 3, 27 patients (36%) in total had anaemia. Of the anaemia cohort, 16 (59.3%) had PNA, 9 (33.3%) had PH, and 2 (7.4%) were asymptomatic. These results can be expressed as ratios 16:9:2=8:4.5:1; therefore,

Table 1. Patient demography and clinical characteristics.

Variable	Total	Groups		
		A	B	C
N	75	30	25	20
Age, months, mean $\pm$ SD	8.3 $\pm$ 5.72 (range, 3–24)	10.8 $\pm$ 19	11.5 $\pm$ 12.8	8.8 $\pm$ 5.1
Gender (female/male)	27/48	9/21	10/15	8/12
Weight, kgs, mean $\pm$ SD	5.9 $\pm$ 3.9 (range, 2.7–17.8)	4.9 $\pm$ 3.2	6.5 $\pm$ 4.8	6.7 $\pm$ 3.4
Ventricular septal defect, cm, mean $\pm$ SD	0.93 $\pm$ 0.31 (range, 0.4–1.6)	1.2 $\pm$ 0.3	0.89 $\pm$ 0.2	0.65 $\pm$ 0.2
Pulmonary hypertension, mmHg, mean $\pm$ SD	25.5 $\pm$ 8 (range, 16–55)	21.2 $\pm$ 3.4	34 $\pm$ 8.2	21.4 $\pm$ 2.7

Table 2. Mean hematologic profile and laboratory results according to age groups.

Variable	Young children (≥ 3 – ≤ 6 months)			Older children (> 6 – ≤ 24 months)			p-value
	A*	B*	C*	A^	B^	C^	
Haemoglobin (g/l; mean $\pm$ SD)	109 $\pm$ 25.1	108.3 $\pm$ 21.2	132.2 $\pm$ 18	109.8 $\pm$ 25.8	117.9 $\pm$ 15.4	133.6 $\pm$ 6.8	*0.04 ^0.008
Mean corpuscular volume (f/l)	76.9 $\pm$ 7.3	85.7 $\pm$ 2.1	83.9 $\pm$ 9	74.6 $\pm$ 5	82.8 $\pm$ 6.6	85.6 $\pm$ 4.8	*0.001 ^0.0003
Mean corpuscular haemoglobin (pg; mean $\pm$ SD)	27 $\pm$ 3.1	30.3 $\pm$ 2.1	28.4 $\pm$ 1.8	33.9 $\pm$ 7.2	29 $\pm$ 2.9	30.4 $\pm$ 2	*0.006 ^0.039
Lactate dehydrogenase (mean $\pm$ SD)	236.8 $\pm$ 76.8	222.4 $\pm$ 61.6	213.6 $\pm$ 61.6	300.9 $\pm$ 119.2	174.3 $\pm$ 50	147 $\pm$ 30	*0.68 ^0.0001
White blood cell ($\times 10^9$ /L; mean $\pm$ SD)	12.5 $\pm$ 5.3	7.8 $\pm$ 2.4	6.9 $\pm$ 0.9	15.4 $\pm$ 5.7	6.7 $\pm$ 1.5	5.9 $\pm$ 2.1	*0.003 ^0.0001
Red blood cell ($\times 10^{12}$ /L; mean $\pm$ SD)	3.8 $\pm$ 0.9	3.6 $\pm$ 0.9	3.8 $\pm$ 0.4	3.2 $\pm$ 0.5	4.3 $\pm$ 0.6	4.8 $\pm$ 0.4	*0.9 ^0.0001

Table 3. Association between age and anaemia prevalence.

Group	N; age (months; mean $\pm$ SD)	Haemoglobin (%)	
		Anaemia	Normal
Young children (≥ 3 – ≤ 6 months; n=42)	19; 4.85 $\pm$ 1.07	45.2	54.8
Older children (> 6 – ≤ 24 months; n=33)	6; 12.69 $\pm$ 6.02	18.2	81.8
Association between complication and anaemia distribution			
		N (%)	
		Anaemia	Normal
A	16; 30	53.3	46.7
B	9; 25	36	68
C	2; 20	10	90

patients with PNA and PH are 8 and 4 times more susceptible to developing anaemia than asymptomatic patients.

Of the cohort, 42 were young children, and of those 19 had anaemia (45.2%), while 24.2% of the older children had anaemia. Haemoglobin intergroup (ANOVA) independent sample t-test was significant ($p < 0.05$). In addition, intergroup *Tukey HSD* test for haemoglobin: A/B ($p > 0.05$), A/C ($p < 0.01$), B/C ($p < 0.01$). The mean white blood cells in patients with PNA was higher and intergroup p-value was significant ($p < 0.05$).

Discussion

Anaemia, defined as haemoglobin (Hb) concentration below the 5th percentile for age at sea-level, is a common complication of a myriad medical conditions often met in the general ward¹. Its aetiology is complex and multifactorial, encompassing intrinsic and extrinsic factors. Both pneumonia (PNA) and pulmonary hypertension (PH) due to cyanotic congenital heart defect (CHD) have been implicated in the occurrence of anaemia^{2,3,7}. In addition,

sporadic reports linking anaemia to PNA or PH amongst patients with acyanotic ventricular septal defect (VSD) have been published.

VSD is the second commonest CHD after bicuspid aortic valve^{4,10}, and solitary cases account for almost 20%. One of the most common defects associated with elevated pulmonary artery pressure is a large VSD. Elevated pulmonary artery pressure in CHD can be due to pulmonary hyper-circulation, pulmonary vasoconstriction, and pulmonary vascular disease, either alone or in combination. In an infant, despite pulmonary pressure being at systemic level, pulmonary vascular resistance is low; therefore, minor shunt easily elicits hyper-circulation^{2,4,7,11}.

PH, defined as mean pulmonary artery pressure of ≥ 25 mmHg at rest as measured by cardiac catheterization in children aged ≥ 3 months, is a serious disorder with a high morbidity and mortality rate². Blood shunt may cause haemolysis due to shear stress and produce free haemoglobin, which in turn depletes nitric oxide leading to endothelial dysfunction, vasoconstriction,

pulmonary oedema and hypoxia. Furthermore, haemolysis produces arginase, which converts L-arginine to ornithine; therefore, bypassing nitric oxide production^{2,9,12}.

PNA, defined as an inflammation of alveoli (with or without pus) due to an infection is a serious morbidity and mortality reason for children (≤ 2 years) with hemodynamic significant VSD^{5,13}. Similar to PH, inflammatory state in PNA causes pulmonary oedema, homeostasis and hypoxia, with subsequent upregulation of erythrocyte synthesis^{8,14}. Prolonged upregulated erythropoiesis in young children with low iron store and limited iron source (exclusive breast milk) can develop low haemoglobin levels¹. In addition, microangiopathic haemolytic anaemia in CHD and PH has been reported³, a complication commonly observed in primary PH. Unlike PH, a number of PNA causatives are known to cause haemolytic and iron deficient anaemia. *Mycoplasma pneumoniae* has been reported to cause severe haemolytic anaemia^{15,16}. In addition, *Klebsiella* is known to compete for iron with host via siderophores⁶.

Our study shows that patients with acyanotic VSD within mean sizes 1.2 ± 0.3 and 0.89 ± 0.2 cm were prone to develop recurrent lower respiratory tract infection and pulmonary vascular disorder. The two pathological conditions primarily share common features including pulmonary oedema, haemostasis and hypoxia, with an immediate non-hemodynamic response in form of increased erythropoiesis. However, unlike PH, toxins from certain causatives (bacteria) in PNA induce haemolysis, while other pathogens compete for iron with the host. Owing to LDH and WBC elevation in group A, it's evident that there was some haemolysis of a certain degree as a result of an infection. Other potential causes include microangiopathic haemolysis in CHD with PH, feeding difficulties and malabsorption. Given the high proportion of anaemia in the 'young children' group, it is logical to assume they were fed exclusively on breast (artificial) milk, possibly limiting the source of iron. From our study, it is evident that diagnosis of hemodynamic significant acyanotic VSD in comorbid with PNA or PH should heighten the suspicion index of anaemia. However, we acknowledge that aetiology of anaemia is multifactorial, and so many intrinsic and extrinsic factors are at play, hence, every case requires a holistic approach.

Limitations

To the best of our knowledge this comparative concept is new; therefore, a larger cohort in a prospective model would validate our findings.

Conclusion

Paediatric patients without hematologic disorders, diagnosed with hemodynamic significant acyanotic VSD in comorbid with PNA or PH are 8 and 4 times susceptible to develop anaemia compared to asymptomatic counterparts. Susceptibility is even high amongst young children (3–6 months).

Ethical considerations

The Shandong Provincial Hospital Ethics Committee approved this study, and waived individual patient consent as the study was based on archived data.

Data availability

Harvard Dataverse: Anaemia in solitary acyanotic ventricular septal defect in comorbid with pneumonia or pulmonary hypertension; a retrospective study of 75 paediatric cases, <https://doi.org/10.7910/DVN/2B328D>¹⁷.

Data are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC0 1.0 Public domain dedication).

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Reviewer Report 15 October 2019

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Raymond N. Haddad

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Firstly, I want to thank The Editorial Team of F1000Research for this opportunity to review the following manuscript.

I want to also thank the authors for recommending as a reviewer for their manuscript. Although this comparative concept is extremely new and interesting, I will generate candid comments which at times may seem overly critical. Please accept these criticisms in the positive spirit in which they are intended. I believe that the manuscript would be suitable for indexing if the comments/questions are addressed and appropriate changes made.

1. The authors in their Introduction largely reviewed the anemia and the contributing factors of PNA and PH which in large part are repeated in the discussion section. For that, I recommend that authors should summarize their introduction while briefly reviewing the role of VSD closure in the anemia (especially when all their patients had repaired defects either surgically or with minimal invasive approach).
2. Authors are encouraged to detail the method of defect repair. When is was performed? Is it early on diagnosis or later in time? The reason for closure especially in small defects? What do they actually mean by minimal invasive closure? Is it percutaneously or using a hybrid approach? Moreover, authors should explain why did they consider PNA as the only lower respiratory tract infection? And diagnosis of PHT should be more clearly detailed and if international guidelines were used reference must be cited. Additionally, where all patients screened for other possible hematological diseases to be excluded from the study?
Table 1 : What does the patients mean by VSD size? is it the LV entry or the RV exit? I advice the authors to mention minimum and maximum values especially in each of the 3 groups for the PHT row as it may seems that some of Group A patients had PHT.
3. Statistics: SPSS version must reported.
4. Table 1 and 2 should be briefly described in the results sections.

5. Table 3 must be just reported in the text.
6. The first 4 paragraphs of the discussion are pure literature review without any relevant discussion with the study results. In fact excessive review could impose more stratified results: should authors report the etiology on the PNA since the described the possible implications of infectious organisms in anemia. Therefore, discussion should focus in some part on the prevalence of anemia in **repaired** VSD (and if possible discussing the timing of closure and its possible effect of the results) while highlighting what is has been previously written by the authors.
7. No changes are needed for the limitations and conclusions section.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pediatrics, Pediatric cardiology, Pediatric interventionnal cardiology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 27 March 2019

<https://doi.org/10.5256/f1000research.19583.r44745>

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Shengli Li

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1. The manuscript is a small-size retrospective study about the prevalence of anaemia in patients with solitary acyanotic VSD in comorbid with PNA or PH; they find that patients with acyanotic VSD in comorbid with PNA or PH were 8 and 4 times more susceptible to develop anaemia compared to asymptomatic counterparts.
2. For the VSD patients with PNA or PH, does the increased incidence of anaemia have any influence on the therapy or clinical management?
3. As the aetiology of anaemia is multifactorial, any intrinsic and extrinsic factors should be analysed in this article. This is crucial.
4. As mentioned above, it suggests that this article needs to be revised before accepting for indexing.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Fetal medicine, prenatal diagnosis of fetal malformations

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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