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Cerebrovascular Events in Adult Patients With Cyanotic Congenital Heart Disease

NASER AMMASH, MD, CAROLE A. WARNES, MD, MRCP, FACC

Rochester, Minnesota

Objectives. **We sought to determine the frequency of spontaneous cerebrovascular events in adult patients with cyanotic congenital heart disease and to evaluate any contributing factors.**

Background. **Cerebrovascular events are a serious complication of cyanotic congenital heart disease in infants and children but are said to be uncommon in adults.**

Methods. **Between 1988 and 1995, 162 patients with cyanotic congenital heart disease (mean age 37 years, range 19 to 70) were retrospectively evaluated for any well documented cerebrovascular events that occurred at ≥18 years of age. Events related to procedures, endocarditis or brain abscess were excluded.**

Results. **Twenty-two patients (13.6%) had 29 cerebrovascular events (1/100 patient-years). There was no significant difference between those with and without a cerebrovascular event in terms of age, smoking history, degree of erythrocytosis, ejection fraction or use of aspirin or warfarin (Coumadin). Patients who had a cerebrovascular event had a significantly increased tendency to develop hypertension, atrial fibrillation, microcytosis (mean corpuscular volume <82) and history of phlebotomy ($p < 0.05$). Even when patients with hypertension or atrial fibrillation were excluded, there was an increased risk of cerebrovascular events associated with microcytosis ($p < 0.01$).**

Conclusions. **Adults with cyanotic congenital heart disease are at risk of having cerebrovascular events. This risk is increased in the presence of hypertension, atrial fibrillation, history of phlebotomy and microcytosis, the latter condition having the strongest significance ($p < 0.005$). This finding leads us to endorse a more conservative approach toward phlebotomy and a more aggressive approach toward treating microcytosis in adults with cyanotic congenital heart disease.**

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Adult patients with cyanotic congenital heart disease are at an increased risk of hyperviscosity secondary to erythrocytosis. One important issue that remains unsettled, however, relates to the risk of stroke or cerebrovascular events in these cyanotic patients. Venous thrombosis and, less commonly, arterial thrombosis with secondary cerebrovascular accidents have been well documented in infants and children with cyanotic congenital heart disease (1,2). This is thought to be primarily related to an increased red blood cell mass, and occasionally, iron deficiency anemia is seen in these patients (1,3–6). Both of these factors have been implicated in increasing the whole blood viscosity, with frequent upper respiratory tract infections, fever and dehydration playing a major contributing role in the development of vessel thrombosis (4,7). Published reports, however, have not all agreed that adult patients with cyanotic congenital heart disease are also at risk of cerebrovascular events or strokes (1). This prompted us to review our experience in the Adult Congenital Heart Disease Clinic to determine the frequency of cerebrovascular events in these patients and to evaluate any contributing risk factors.

From the Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

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Address for correspondence: Dr. Carole A. Warnes, Division of Cardiovascular Diseases and Internal Medicine, West 16A, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905.

Methods

Patient selection. We performed a retrospective review of the medical and surgical records of all patients who attended the Adult Congenital Heart Disease Clinic since 1988. This included patients who had complex repair before their first visit, in which case clinical and neurologic events had to be well documented before their surgical intervention. Patients were included in the study if they had 1) a congenital anomaly consistent with cyanotic congenital heart disease such as tetralogy of Fallot, a single ventricle or Eisenmenger's syndrome; 2) clinical cyanosis with a hemoglobin level ≥14.5 g/dl; 3) no history of carotid artery disease; and 4) no primary intracranial pathology such as a vascular malformation.

One hundred sixty-two patients 19 to 70 years old (mean 37 ± 11.6) met all four of the above criteria. Patients were divided into two groups: Group I ($n = 140$) included those patients who had no history suggestive of a cerebrovascular event, and Group II ($n = 22$) included those who had a well documented cerebrovascular event manifested by a transient ischemic attack, a reversible ischemic neurologic deficit or a completed infarct. Transient ischemic attack was defined as a temporary neurologic deficit corresponding to the anatomic distribution of a carotid or vertebral artery that lasted <24 h without any residual deficit. Reversible ischemic neurologic deficit was defined as a prolonged, fully reversible neurologic deficit that could have lasted from 1 day to a few weeks. The

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completed infarct or stroke was defined as a prolonged neurologic event that may or may not have been followed by only partial recovery within days to weeks, and preferably with a computed tomographic and/or magnetic resonance imaging (MRI) scan documenting the brain infarct.

Patients with cerebrovascular events were excluded from our analysis if the events occurred before 18 years of age (n = 2). To determine the frequency of spontaneous cerebrovascular events, patients were excluded if the events were related to procedures such as cardiac catheterization or catheter ablation (n = 1), active infective endocarditis or brain abscess (n = 2). Patients were also excluded if the cerebrovascular events were of unknown origin, such as from dizziness, generalized weakness or syncope of unclear etiology (n = 3).

Clinical variables. The following clinical information and variables were obtained for all 162 patients—age at the time of the last clinic visit, gender, number of years of follow-up since age 18 years, history of systemic hypertension, tobacco abuse or antecedent atrial fibrillation. Information related to a history of iron deficiency anemia, therapeutic phlebotomy or intake of aspirin or warfarin (Coumadin) was also recorded. In addition, the degree of erythrocytosis (hemoglobin and hematocrit) as well as mean corpuscular volume, oxygen saturation (when available) and ejection fraction of the systemic ventricle were reviewed. For patients with no history of cerebrovascular event (Group I), we chose those values obtained during the last clinic visit as well as the patients' most recent assessment of ejection fraction and oxygen saturation. For patients with a history of cerebrovascular events (Group II), we recorded hemoglobin, hematocrit, mean corpuscular volume and ejection fraction at the time of the cerebrovascular event or shortly before it. When such data were unavailable, we reviewed the laboratory profile and selected those values that were obtained closest to the cerebrovascular event.

Statistical analysis. Unpaired, two-sample *t* test analysis was performed for comparison of continuous variables such as ejection fraction between patients in Group I and Group II after appropriate testing for normality. Chi-square analysis was performed to compare discrete variables between the two groups. Data presented are mean value ± SD. To assess multivariate relations between patient characteristics and a history of cerebrovascular events, multiple logistic regression analysis was performed with a history of cerebrovascular event as the dependent variable. Only variables with an apparent univariate association with cerebrovascular events, as well as age and gender, were considered.

Results

One hundred sixty-two patients (86 men, 76 women) aged 19 to 70 years (mean 37) were included in our study (Table 1). Fifty-one patients (31.5%) were seen only once, when they met the inclusion criteria, including those who were referred for surgical intervention and subsequently became acyanotic. Because of the retrospective nature of this review, follow-up was available for up to 51 years (mean 19) from the entry age of 18 years. The remaining 111 patients (68.5%) were evaluated more than once, and their follow-up evaluations ranged from 1 to >30 years. Total follow-up was 3,135 patient-years (mean 19.35 ± 11.8).

Table 1. Clinical Variables

	Group I (no CVE) (n = 140)	Group II (CVE) (n = 22)	Total (n = 162)	p Value
Age (years)				
Range	19–70	21–57	19–70	
Mean ± SD	37 ± 12	40 ± 12	37 ± 12	0.226
Male/female	73/67	13/9	86/76	0.54
Diagnosis				
Complex	49	8	57	
Eisenmenger's syndrome	45	6	51	
Pulmonary atresia	17	3	20	0.94
Ebstein	22	3	25	
Tetralogy of Fallot	6	2	8	
PS/VSD	1	0	1	
Follow-up (years)				
Range	1–52	3–49	1–52	
Mean ± SD	18.9 ± 11.7	22.2 ± 12.1	19.4 ± 11.8	0.23

Unless otherwise indicated, data presented are number of patients. CVE = cerebrovascular event; PS = pulmonary stenosis; VSD = ventricular septal defect.

Cerebrovascular events. One hundred forty patients (Group I) had no history suggestive of cerebrovascular events occurring after 18 years of age, and 22 patients (13.6%, Group II) had a total of 29 cerebrovascular events, including 19 transient ischemic attacks, 4 reversible ischemic neurologic deficits and 6 strokes. Six of these patients had more than one event, including one patient who had three events. The neurologic symptoms associated with these cerebrovascular events included 18 events in which patients had signs and symptoms suggestive of hemiplegia, hemiparesis or sensory deficit, or a combination of these. Eight events were associated with visual disturbance such as diplopia and homonymous hemianopsia. Three events were manifested by amaurosis fugax, and another three events were associated with speech disturbance. There was one cerebrovascular event manifested by a lacunar infarct documented by computed tomography of the brain.

A normal computed tomographic and/or MRI scan of the brain was documented in 12 (52%) of 23 transient ischemic attacks or reversible ischemic neurologic deficits. No radiographic documentation was available for the remaining transient ischemic attacks and reversible ischemic neurologic deficits (n = 11). In contrast, all five patients who had a history of stroke did have a computed tomographic and/or MRI scan of the brain during their events. Four patients had one brain infarct each, and one patient had two infarcts. Five of these examinations showed hemispheric infarct, and one was completely normal. In addition, four of these five patients who had a total of six infarcts had a residual neurologic deficit, and one death related to complications of the infarct occurred.

The congenital anomalies associated with cyanotic congen-

Table 2. Hemodynamic and Hematologic Variables

	Group I (no CVE) (n = 140)	Group II (CVE) (n = 22)	p Value
Continuous variable			
EF (%)			
Range	20–70	34–65	0.707
Mean ± SD	53 ± 9.8	52 ± 8.9	
Hemoglobin			
Range	14.5–23.5	14.5–23.1	0.081
Mean ± SD	17.7 ± 1.86	18.4 ± 2.2	
Hematocrit			
Range	41.7–70.1	41.3–63.1	0.11
Mean ± SD	53.3 ± 6.0	54.4 ± 6.7	
MCV			
Range	57.4–104.5	68.6–89.7	0.345
Mean ± SD	87.8 ± 9.7	85.7 ± 9.8	
Discrete variable			
Hypertension			
Yes	4	3	0.021
No	136	19	
Atrial fibrillation			
Yes	13	6	0.015
No	127	16	
Smoking			
Yes	17	2	0.68
No	123	20	
Phlebotomy			
Yes	35	11	0.016
No	105	11	
Iron deficiency anemia/ microcytosis			
Yes	30	11	0.004
No	110	11	
Antiplatelet intake			
Yes	17	2	0.68
No	123	20	
Warfarin intake			
Yes	17	1	0.29
No	123	21	

Unless otherwise indicated, data presented are number of patients. CVE = cerebrovascular event; EF = ejection fraction; MCV = mean corpuscular volume.

ital heart disease in these patients are shown in Table 1. Fifty-seven patients (35.2%) had complex congenital heart disease such as single ventricle or double-outlet right ventricle. Fifty-one patients (31.5%) had Eisenmenger's syndrome secondary to an atrial septal defect, a ventricular septal defect, patent ductus arteriosus or truncus arteriosus. The clinical variables of these two groups of patients are also shown in Table 1. There was no statistically significant difference between Group I and Group II patients in terms of age, gender, mean years of follow-up or anatomic diagnosis.

A detailed comparison of the hemodynamic and hematologic variables between the two groups is shown in Table 2. There was no difference in the mean ejection fraction of the systemic ventricle between the two groups. Group I patients had a mean ejection fraction of 53 ± 9.8%, whereas Group II patients had a mean ejection fraction of 52 ± 8.9%. Oxygen saturation measurement was available in 75 patients in Group I (range 60% to 90%, mean 80%) and 11 patients in Group II (range 66% to 88%, mean 80%).

Systemic hypertension. Because this cohort is relatively young (mean age 37 years), it is not surprising that the incidence of systemic hypertension is low (7 [4.3%] of 162). When comparing those patients with hypertension in Group I versus Group II, there appeared to be an increased risk of cerebrovascular events associated with hypertension (4 of 140 vs. 3 of 22, p = 0.021) (Table 2). However, we recognize the small number of patients with a history of hypertension in our study group. When patients with such a history (n = 7) were excluded from the analysis, the risk of cerebrovascular events continued to be high (14%), with 19 patients who had cerebrovascular events versus 136 patients who did not.

Atrial fibrillation. A total of 19 patients had documented atrial fibrillation, paroxysmal in 17 (11 in Group I, 6 in Group II) and chronic in 2 (Group I). There was a statistically significant difference between Group I and Group II in terms of history of atrial fibrillation (p = 0.015) (Table 2). When the seven patients with hypertension were excluded from the study, atrial fibrillation remained an important risk factor for cerebrovascular events (p = 0.033, 13 of 136 in Group I vs. 5 of 19 in Group II). However, when patients with atrial fibrillation were excluded from the study, the incidence of cerebrovascular events remained high (12.6%), with 16 patients who had an event and 127 patients who did not.

Tobacco use. Among the 162 patients, 143 (88.3%, 123 in Group I and 20 in Group II) never smoked tobacco, although 19 (11.7%, 17 in Group I and 2 in Group II) did at some time during their life, including 12 patients who continued to do so at the time of their last clinic visit (Table 2). Chi-square analysis showed no statistical difference between Group I and Group II in terms of tobacco use, and therefore smoking was not associated with an increased risk of cerebrovascular events in this patient group.

Hematologic profile. The mean hemoglobin level in our study group was 17.8 g/dl, with a mean hematocrit of 43.3% and a mean corpuscular volume of 87.5. Unpaired *t* test analysis with a 95% confidence limit showed no statistical difference (p = 0.81) between Group I and Group II in terms of hemoglobin and hematocrit (Table 2). Similarly, the mean red blood cell mean corpuscular volume did not differ significantly between Group I and Group II (Table 2).

Forty-one patients demonstrated iron deficiency anemia with microcytosis (mean corpuscular volume < 82). This was either secondary to phlebotomy, gastrointestinal bleeding or menorrhagia. Eleven of these patients had a cerebrovascular event, demonstrating the very strong association between iron deficiency anemia with microcytosis and a history of cerebrovascular events (p = 0.004) (Table 2). This statistically significant association persisted even when patients with hypertension and atrial fibrillation were excluded from the analysis (28 of 123 in Group I vs. 8 of 14 in Group II).

Phlebotomy. It is not our policy to recommend therapeutic phlebotomy for patients with cyanotic congenital heart dis-

ease who present with significant erythrocytosis (hemoglobin >20 g/dl or hematocrit >65%), unless they have symptoms of hyperviscosity. Nonetheless, 46 (28.4%) of the 162 patients had a history of phlebotomy; most of the procedures were performed before their referral to our center. Eleven of these patients had cerebrovascular events, although 35 patients did not. A chi-square comparison between Group I and Group II showed a significantly increased risk of cerebrovascular events after therapeutic phlebotomy (35 of 140 vs. 11 of 22, $p = 0.016$).

Antiplatelet and warfarin intake. A total of 19 patients were taking either aspirin or dipyridamole, including 17 patients in Group I and 2 patients in Group II. Another 18 patients were taking warfarin, including 17 patients in Group I and only 1 patient in Group II. The indication for chronic anticoagulation with warfarin was atrial fibrillation in five patients, pulmonary hypertension in five, a history of pulmonary embolism in two, a history of lower extremity edema/varicosities in two, mechanical valve prosthesis in one and marked depression of systemic ejection fraction in one. One patient had been placed on warfarin after a syncopal episode of unclear etiology, but the medication was discontinued on his first clinic visit. All of these 17 patients belonged to Group I. Only one patient was taking warfarin at the time of the cerebrovascular event. There was no statistically significant decrease in the incidence of cerebrovascular events in patients who were taking either antiplatelet agents or warfarin. Subsequent analysis of 21 patients with atrial fibrillation or flutter (15 in Group I and 6 in Group II) also showed no statistically significant decrease in the incidence of cerebrovascular events associated with chronic anticoagulation ($p > 0.5$).

In a multiple logistic regression analysis, hypertension ($p = 0.040$), atrial fibrillation ($p = 0.012$) and microcytosis ($p = 0.004$) were significantly independently related to cerebrovascular events. When phlebotomy was added to this model, the significance was borderline ($p = 0.115$).

Discussion

Stroke is generally considered a disease of the elderly, with only 5% of cases occurring in patients <45 years old (8). However, the emotional, psychological and economic impact of cerebrovascular events is potentially devastating, and so stroke prevention is very important. The association between hematologic disorders and stroke is well established. Patients with a primary red blood cell disorder such as polycythemia rubra vera are at an increased risk of cerebrovascular events, the majority of which are cerebral infarcts related to vessel occlusion rather than intracranial hemorrhage (4,9). In contrast, patients with cyanotic heart disease do not have polycythemia but have an increase in red cell mass. This secondary erythrocytosis may increase blood viscosity and thereby reduce cerebral blood flow (4,7,10). As a result, children with cyanotic congenital heart disease are at increased risk of cerebrovascular events. The vast majority of these events are cerebral venous rather than arterial thrombosis, and the reported incidence varies from 1.6% to 20% (3,11).

Although the association between secondary erythrocytosis and the increased risk of cerebrovascular event is well documented in infants and children with cyanotic congenital heart disease, recent reports have challenged this finding in the adult population. Perloff et al. (1) found no increased risk of stroke in 112 patients (mean age 36 ± 11.7 years, range 19 to 74) with cyanotic congenital heart disease followed continuously from 1 to 12 years (total 748 patient-years). Our study is somewhat similar in terms of patient selection. However, there are two major differences between the two studies. First, our study retrospectively evaluated any well documented cerebrovascular event since the age of 18 years, including those that occurred before the patients started attending the Adult Congenital Heart Disease Clinic, as well as those events that occurred before any surgical intervention corrected the cyanosis. Thus, we report a longer duration of follow-up (3,135 vs. 748 patient-years). Second, we did not exclude patients who had independent risk factors for stroke, such as tobacco use, hypertension and atrial fibrillation, from our initial analysis. Nonetheless, when these patients were excluded, the incidence of cerebrovascular events remained high (14.7%), with 16 patients who had an event compared with 109 patients who did not. Our study is the first to show that the association between cyanotic congenital heart disease and cerebrovascular events is real not only in children but also in adults (incidence 13.6%, 0.92 events per patient per 100 patient-years). More important, our study has shown that there are four independent risk factors associated with the development of cerebrovascular events in adults—namely, systemic hypertension, atrial fibrillation, therapeutic phlebotomy and iron deficiency anemia/microcytosis.

Hypertension. Hypertension and atrial fibrillation are well known independent risk factors for stroke. The number of patients with systemic hypertension is small (n = 7 [4.3%]), but there is reason to believe that patients with cyanotic congenital heart disease would benefit from adequate blood pressure control just like patients with other conditions, provided vasodilator drugs, which might increase right-to-left shunt and worsen cyanosis, are avoided.

Atrial fibrillation. Numerous studies have demonstrated a clear benefit from the use of anticoagulation, and to a lesser extent, from antiplatelet agents, in reducing the risk of cerebrovascular events in patients with atrial fibrillation (12–14). Subgroup analysis of all 19 patients with atrial fibrillation in our group (13 in Group I and 6 in Group II) showed no significant difference from those who were treated with long-term anticoagulation in terms of risk of cerebrovascular event, and similar results were found with antiplatelet agents. However, the small number of patients in this subgroup precludes any statistically significant conclusion. In view of the potential hemorrhagic side effects of both antiplatelet agents and warfarin in these patients, who are also known to be at increased risk of bleeding (3,7), decisions regarding these agents must be individualized.

Phlebotomy. Therapeutic phlebotomy, which has long been used in patients with cyanotic congenital heart disease in the hope of reducing the risk of hyperviscosity and stroke, poses a potential hazard because of the possible risk of decompensated erythropoiesis and iron deficiency anemia (1,15). In this study, 11 (50%) of the 22 patients with a history of cerebrovascular events had had a phlebotomy. Several investigators have demonstrated that iron deficiency anemia and microcytosis pose an increased risk of cerebrovascular events in children with cyanotic congenital heart disease (2,3,5,16). This study is the first to report an increased risk in adults. Iron-deficient red blood cells are less deformable than normal red blood cells and do not pass through the microcirculation as readily as iron-replete cells (2,7). This in itself will further increase whole blood viscosity and the risk of cerebrovascular events in patients with cyanotic congenital heart disease (2,4,7).

Iron deficiency. Adult patients with cyanotic congenital heart disease are at risk of depleting their iron stores and developing iron deficiency anemia either because of a phlebotomy or sometimes because of heavy menses or gastrointestinal bleeding (3,7,16,17). Certainly the development of microcytosis poses the greatest risk for a cerebrovascular event. Our study demonstrates this clearly, as microcytosis was present in 11 of 22 patients with a cerebrovascular event. This stresses the importance of regular follow-up of the red blood cell indices in this patient group, especially if they have a history of bleeding (gastrointestinal or gynecologic) or have had a recent phlebotomy.

Therapeutic implications. This study is the first to show a clear, statistically significant increase in the incidence of cerebrovascular events in adults with cyanotic congenital heart disease and iron deficiency anemia and/or microcytosis. Even when patients with hypertension or atrial fibrillation, or both, were excluded from the study, microcytosis was indeed the strongest risk factor associated with cerebrovascular events. This study therefore suggests a more aggressive approach to treating iron deficiency anemia or microcytosis, or a combination, with iron replacement when the mean corpuscular volume is <82. Restoring normocytosis should decrease the risk of cerebrovascular events. To avoid a rebound response by the bone marrow, however, low dose ferrous sulfate (325 mg/day) is suggested with follow-up blood counts at 1 week. Iron replacement should be discontinued as soon as the hemoglobin starts to rise (15). This study also underscores the need to avoid a phlebotomy unless absolutely necessary (1) (hemoglobin >20 g/dl or hematocrit >65%). Furthermore, when a phlebotomy is performed, it should be accompanied by isovolumic fluid replacement, and the red blood cell indices should be closely monitored to prevent microcytosis and iron deficiency anemia (15). In contrast to the study by Perloff et al. (1), this study demonstrates that adult cyanotic patients who had neither phlebotomy nor microcytosis from any cause are still at significant risk of cerebrovascular events (7 [7.7%] of 91 patients).

References

1. Perloff JK, Marelli AJ, Miner PD. Risk of stroke in adults with cyanotic congenital heart disease. Circulation 1993;87:1954–9.
2. Cottrill CM, Kaplan S. Cerebral vascular accidents in cyanotic congenital heart disease. Am J Dis Child 1973;125:484–7.
3. Phornphutkul C, Rosenthal A, Nadas AS, Berenberg W. Cerebrovascular accidents in infants and children with cyanotic congenital heart disease. Am J Cardiol 1973;32:329–34.
4. Grotta JC, Manner C, Pettigrew C, Yatsu FM. Red blood cell disorders and stroke. Stroke 1986;17:811–7.
5. Linderkamp O, Klose HJ, Betke K, et al. Increased blood viscosity in patients with cyanotic congenital heart disease and iron deficiency. J Pediatr 1979;97:567–9.
6. Shmid-Schonbein H, Wells R, Goldstone J, et al. Influence of deformability of human RBC upon blood viscosity. Circulation 1969;25:131–43.
7. Territo MC, Rosove M, Perloff J. Cyanotic congenital heart disease: hematologic management. In: Perloff J, Child JS, editors. Congenital Heart Disease in Adults. Philadelphia: W.B. Saunders, 1991:93–103.
8. Bell RD. Stroke in young adults. Intern Med 1995;16:39–46.
9. Saxena VK, Brands C, Crols R, Moens E, Marien P, deDeyn PP. Multiple cerebral infarctions in a young patient with secondary thrombocytopenia due to iron deficiency anemia. Acta Neurol 1993;15:297–302.
10. Thomas DJ, Marshall J, Russell RW, et al. Cerebral blood flow in polycythemia. Lancet 1977;2:161–3.
11. Mito T, Pereyra P, Becker LE. Neuropathology in patients with congenital heart disease and Down syndrome. Pediatr Pathol 1991;11:867–77.
12. Sacco RL, Boden-Albala B, Lipset CH. Stroke prevention: importance of risk factors. Intern Med 1995;16:13–38.
13. Stroke Prevention in Atrial Fibrillation Investigators. Stroke prevention in atrial fibrillation study: final results. Circulation 1991;84:527–39.
14. Connolly SJ, Laupacis A, Gent M, et al. Canadian Atrial Fibrillation Anticoagulation (CAFA) study. J Am Coll Cardiol 1991;18:349–55.
15. Perloff JK, Rosove M, Child JS, Wright GB. Adults with congenital heart disease: hematologic management. Ann Intern Med 1988;109:406–13.
16. Amitai Y, Blieden L, Shemtov A, Neufeld H. Cerebrovascular accidents in infants and children with congenital cyanotic heart disease. Isr J Med Sci 1984;20:1143–5.
17. Territo MC, Rosove MH. Cyanotic congenital heart disease: hematologic management. J Am Coll Cardiol 1991;18:320–2.