independent predictors using randomized controlled trials or analysis of patient-level data in observational studies.

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Cerebrovascular Events in Adult Patients With Cyanotic Congenital Heart Disease

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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.

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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.

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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).

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Thromboembolic problems after the Fontan operation.

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Abstract

One of the major causes of morbidity and mortality after the Fontan operation is thromboembolic events (TE). To assess the current knowledge of TE after Fontan surgery, a comprehensive MEDLINE search of the English literature from 1971 to 2000 was conducted using the key words Fontan, univentricular **heart**, children, **thrombosis**, **congenital heart disease**, cavopulmonary, and palliation. Other relevant publications were identified from bibliographies of the literature retrieved. Fifty-one studies were identified and analyzed for incidence, potential morbidity and mortality, risk factors, prophylactic options, and risk/benefit ratio of prophylactic anticoagulation as relates to TE after Fontan surgery. There were 23 case reports, 13 retrospective cohort studies that included some details about TE among other reported outcomes after Fontan procedures, eight retrospective cohort studies in which TE was the primary outcome measure, and seven articles reporting cross-sectional point surveys, only three of which directly surveyed TE as an outcome. Based on an analysis of the current literature, there is insufficient evidence to make clear recommendations about optimal anticoagulant prophylaxis at this time. Multicenter randomized controlled trials comparing prophylactic antiplatelet with anticoagulation therapies are needed to provide rational scientific guidelines for future management of Fontan patients.

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Thrombosis in Pediatric Cardiac Patients

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ABSTRACT

Cardiac disease and thrombosis are intimately related in adults, but primary myocardial infarction in children is rare. Homozygous familial hyperlipidemia occurs in approximately 1 million children, and causes severe coronary artery disease during childhood. Kawasaki's disease is an acquired inflammatory disorder, which, if untreated, leads to coronary artery aneurysms and subsequent myocardial infarction. The current understanding of the pathophysiology and management of these conditions is discussed. More commonly, the relationship between cardiac disease in children and thrombosis is that children being treated for congenital structural cardiac disease develop iatrogenic thrombosis, most commonly precipitated by central venous access. The epidemiology of common treatment-induced thrombosis is described, and management guidelines presented. Finally, many cardiac surgical procedures increase the risk of thrombosis, and prophylactic antithrombotic therapy is commonly used. The current evidence for prophylaxis in different clinical situations is presented. Additional study is required in all areas to improve the outcome for children affected by cardiac disease and thrombosis.

KEYWORDS

Children - thrombosis - myocardial infarction - congenital heart disease

Risk of Stroke in Adults With Cyanotic Congenital Heart Disease

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Background. Adults with cyanotic congenital heart disease and elevated hematocrit levels are often phlebotomized because of an assumed risk of cerebral arterial thrombotic stroke. Whether a relation exists between hematocrit level, symptomatic erythrocytosis (hyperviscosity), and stroke remains to be established in this patient population.

Methods and Results. Accordingly, 112 cyanotic patients 19–74 years old (mean, 36±11.7 years) in the UCLA Adult Congenital Heart Disease Center Registry were selected for study by virtue of continuous observation for 1–12 years (total, 748 patient-years). Patients with independent risk factors for embolic or vasospastic stroke were excluded. The study patients were then divided into two groups: 1) compensated erythrocytosis (stable hematocrit levels of 46.0–72.7% [mean, 57.5±7.2%], iron replete, absent or mild hyperviscosity symptoms), and 2) decompensated erythrocytosis (unstable rising hematocrit levels of 61.5–75.0% [mean, 69.5±10.6%], iron deficiency, marked-to-severe hyperviscosity symptoms). No patient with either compensated or decompensated erythrocytosis, irrespective of hematocrit level, iron stores, or the presence, degree, or recurrence of cerebral hyperviscosity symptoms, progressed to clinical evidence of a completed stroke (cerebral arterial thrombosis with brain infarction).

Conclusions. Because a risk of stroke caused by cerebral arterial thrombosis was not demonstrated, because the circulatory effects of phlebotomy are transient, and because of the untoward sequelae of phlebotomy-induced iron deficiency, we recommend phlebotomy for the temporary relief of significant, intrusive hyperviscosity symptoms but not for the hematocrit level per se. According to our data, phlebotomy is not warranted to reduce an assumed risk of stroke because that risk did not materialize. (*Circulation* 1993;87:1954–1959)

KEY WORDS • congenital heart disease • stroke • blood cells • hemodynamics

A number of lines of reasoning have been used to argue in favor of linking elevated hematocrit levels (red cell mass) to cerebral infarction. In 1951, Berthrong and Sabiston[1] called attention to cerebral infarcts in cyanotic infants and theorized that the pathogenesis might include in situ thromboses. An increase in red cell mass was then incriminated as the commonest cause of a variety of hyperviscosity syndromes,[2] and the hematocrit level was subsequently emphasized as a risk factor in cerebral infarction.[3] Significant inverse relations have been reported between cerebral blood flow and hematocrit levels and between cerebral blood flow and hyperviscosity.[4,5] In polycythemia rubra vera, vascular occlusive events are common and most often take the form of cerebral thromboses,[6] with a strong positive correlation between hematocrit levels and vascular occlusive episodes.[7] There is a convincing association between cerebrovascular accidents and iron deficiency in young children with cyanotic congenital heart disease.[8–11] Textbook literature reflects a conventional wisdom, warning that in cyanotic congenital heart disease, hematocrit levels that are "too high" increase the risk of cerebrovascular accidents, making reduction of the hematocrit level therapeutically important.[12] What is "too high" is seldom clearly stated, and the criteria for phlebotomy are seldom adequately defined.[13] It has further been argued that in secondary polycythemia, hematocrit levels >60% are detrimental and should be reduced by phlebotomy because overcompensation may impair regional blood flow, particularly in the cerebral circulation.[14,15] In adults with elevated hematocrit levels, impaired alertness reportedly improved significantly after phlebotomy,[16] and in children, adolescents, and young adults with cyanotic congenital heart disease and elevated hematocrit levels, headaches decreased after phlebotomy.[17] It is well to bear in mind, however, that in cyanotic iron-deficient infants and young children, the cerebrovascular occlusive events are venous, not arterial,[9,10] and during the erythrocytotic phase of polycythemia rubra vera, treatment with phlebotomy alone is associated with a statistically significant increase in the risk of thrombotic complications including cerebral infarction, a risk that increased in parallel with the frequency of phlebotomy.[6] Golde et al[18] cautioned against using hematocrit levels per se as the criterion for phlebotomy in patients with secondary erythrocytosis. The efficacy of phlebotomy in adults with cyanotic congenital heart

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disease presupposes an increased risk of stroke caused by thrombotic cerebral infarction, but that risk has not been systematically examined. Therefore, we sought to determine the risk and to ascertain whether or not a relation exists between hematocrit levels, red blood cell indexes, and cerebral arterial thrombosis in adults with cyanotic congenital heart disease.

Methods

At the time of our data analysis, the UCLA Adult Congenital Heart Disease Center had in its registry 775 patients, of whom 165 were cyanotic. The study comprised 112 cyanotic patients 19–74 years old (mean, 36±11.7 years) who have been under continuous observation for 1–12 years (total, 748 patient-years). Inclusion criteria were cyanosis, arterial oxygen desaturation (hypoxemia), and an erythrocytotic response that generated a hematocrit level >45%. Excluded were patients observed for <1 year, those lost to follow-up, and those with independent risk factors for embolic or vasospastic stroke: atrial fibrillation, lower extremity varicosities (potential sources of paradoxical emboli), or severe migraine headaches.[19,20] Also excluded were two clinically acyanotic or minimally cyanotic patients with Fallot's tetralogy, pulmonary atresia, abundant aortic-to-pulmonary collaterals, and hematocrit levels <45%; these two patients did not conform to the inclusion criterion of erythrocytosis in response to hypoxemia (cyanosis).

Patients were divided into two hematologic groups as previously reported[21–23]: "compensated" erythrocytosis and "decompensated" erythrocytosis, defined in terms of erythrocyte indexes and hyperviscosity symptoms. Patients with compensated erythrocytosis established equilibrium hematocrit levels in iron-replete states and had absent, mild, or moderate hyperviscosity symptoms even at high hematocrit levels occasionally >70%. Patients with decompensated erythrocytosis failed to establish equilibrium conditions, manifested unstable, rising hematocrit levels that were poorly controlled by negative feedback inhibition, and experienced marked-to-severe hyperviscosity symptoms. For the purpose of defining the two hematologic groups, hyperviscosity symptoms were those that preceded phlebotomy. Hematocrit levels were based on automated blood counts because microhematocrit centrifugation methods result in plasma trapping and falsely elevated levels.[23]

The presence and degree of cerebral hyperviscosity symptoms were determined by information from a formalized questionnaire[21,22] (Table 1) that focused on headache, faintness, dizziness, light-headedness, altered mentation (impaired alertness, a sense of distance or dissociation), visual disturbances (diplopia, blurred vision), scotoma, tinnitus, and numbness or paresthesia (fingers, toes, lips). Symptoms were graded as absent, mild (present without interfering with normal activities), moderate (interfering with some but not most activities), and marked-to-severe (interfering with most if not all activities).[21,22] Myalgias (including thoracic and occasionally abdominal muscles) and muscle weakness may reflect hyperviscosity but not cerebral hyperviscosity. Gouty arthritis (associated with urate metabolism) and arthralgias (probably associated with hypertrophic osteoarthropathy) do not reflect hyperviscosity and were therefore not included in hyperviscosity symptoms (Table 1).

Because the risk of stroke in adults with cyanotic congenital heart disease is the central concern of this article, precise definition of the various types of stroke is necessary as the backdrop against which assessment can be judged. Stroke is used herein as a descriptive term for a group of disorders characterized by the sudden onset of a neurological deficit caused by ischemia or hemorrhage of the brain or some portions of the brain or brainstem.[24] Relevant to this study are ischemic strokes caused by thrombotic occlusion of a cerebral artery or its branches. Distinctions were made among transient ischemic attacks, reversible ischemic neurological deficits, strokes in evolution, completed strokes with brain infarction, and hemorrhagic strokes.[24] Transient ischemic attacks originating in either the carotid or vertebrobasal distribution are defined as temporary neurological deficits of vascular origin with rapid onset, brief duration (a few minutes to an hour and no more than 24 hours by general consensus), with swift and complete resolution.[24] The significance of transient ischemic attacks is that they may be harbingers of stroke, especially in patients with atherosclerotic cerebrovascular disease.[24] Reversible ischemic neurological deficit is a term applied to an event that is similar to a transient ischemic attack but that partially persists for more than 24 hours, resolving completely within days or weeks.[24] Stroke in evolution is defined as a progressive neurological impairment over a period of several hours or days. Completed stroke (brain infarction) results from a thrombotic or an embolic occlusion of a cerebral artery or from occlusion of a venous sinus, with maximum neurological deficit acquired at the onset and with partial recovery over days, weeks, or months. Hemorrhagic strokes are most commonly caused by subarachnoid hemorrhage and less commonly by intracranial hemorrhage.

Results

In total, 101 patients had compensated erythrocytosis, with hematocrit levels that ranged from 46.0% to 72.7% (mean, 57.5±7.2%) and mean corpuscular volumes of 89.8±9.1 (Table 2). Eleven patients had decompensated erythrocytosis, with hematocrit levels that ranged from 61.5% to 75.0% (mean, 69.5±10.6%), and mean corpuscular volumes of 81.4±6.1 (Table 2). There was virtually no overlap between symptoms of hyperviscosity (Table 1) and symptoms of transient ischemic attacks (Table 3). No patient with either compensated or decompensated erythrocytosis progressed to clinical evidence of cerebral arterial thrombosis with brain infarction (completed stroke) irrespective of the frequency or degree of hyperviscosity symptoms or the duration of follow-up. Other symptoms of transient ischemic attacks, namely, cortical blindness, tinnitus, aphasia, focal motor or sensory deficits (facial or upper or lower extremity), dysarthria, dysphagia, or changes in gait (ataxia, vertigo, or drop attacks) did not occur. Amaurosis fugax was experienced by only one patient, a 28-year-old woman with iron-deficient (decompensated) erythrocytosis. The amaurosis fugax recurred on four occasions in as many months at hematocrit levels that ranged from 63% to 73%.

If patients with compensated erythrocytosis developed new hyperviscosity symptoms or experienced an

TABLE 1. Cyanotic Congenital Heart Disease Questionnaire

Presence and degree of symptoms

0 —Absent: Does not bother you at all
1 —Mild: Bothers you without interfering with normal activities
2 —Moderate: Interferes with some but not most activities
3 —Marked-to-Severe: Interferes with most or all activities

Symptoms	Absent (0)	Mild (1)	Moderate (2)	Marked-to-severe (3)
Erythrocytosis				
Headache				
Faintness, dizziness, light-headedness				
Altered mentation, impaired alertness, a sense of distance or dissociation				
Visual disturbances (blurred vision), scotoma				
Paresthesia of fingers, toes, or lips				
Tinnitus				
Fatigue, lassitude				
Myalgias, muscle weakness				
Hemorrhagic diathesis				
Easy bruising (fragile skin)				
Gingival bleeding				
Hemoptysis				
Epistaxis				
Heavy menses				
Traumatic bleeding (accidental injury, surgery)				
Urate metabolism				
Gouty arthritis				
Osteoarthropathy				
Arthralgias				

In general, how are you feeling *today* compared with the recent past? Better ___ Worse ___ Same ___

Do you take aspirin? _____ Are you taking vitamins that might contain iron? _____

increase in previously stable mild to moderate symptoms, follow-up was shortened to monthly until the symptoms abated or, uncommonly, became sufficient to warrant phlebotomy for temporary relief. In these patients, phlebotomy was seldom performed at intervals of <1 year. Patients with decompensated erythrocytosis required reassessment at relatively short intervals varying from monthly to every 2–3 months. Phlebotomy for temporary relief of markedt-to-severe hyperviscosity symptoms was performed at intervals of 3–6 months.

The neurological symptoms manifested by study patients were those attributed to hyperviscosity and listed in Table 1. Symptoms of transient ischemic attacks listed in Table 3 did not occur irrespective of the duration of follow-up and whether or not the erythrocytosis was compensated or decompensated. The only exception was the single patient who experienced amaurosis fugax (see above). Patients who manifested neurological deficits in response to independent risk factors for embolic or vasospastic stroke were, by definition, not included in the study (see "Methods").

TABLE 2. Hematologic Groups

	Compensated erythrocytosis (n=101)	Decompensated erythrocytosis (n=11)	p
Hematocrit (%)			
Range	46.0–72.7	61.5–75.0	
Mean±SD	57.5±7.2	69.5±10.6	<0.001
Hemoglobin (g/dL)	18.9±2.4	20.8±1.6	<0.001
Mean corpuscular volume (fL)	89.8±9.1	81.4±6.1	<0.001
Phlebotomy (%)	20	80	

TABLE 3. Symptoms of Transient Ischemic Attacks

Carotid distribution
Hemiparesis and/or hemisensory deficit
Amaurosis fugax
Aphasia
Vertebrobasilar distribution (brainstem dysfunction)
Hemiparesis and/or hemisensory deficit
Diplopia
Dysarthria
Dysphagia
Ataxia
Drop attacks
Cortical blindness

Discussion

In all, 112 adults with cyanotic congenital heart disease were observed for a total of 748 patient-years. There were no clinically overt cerebrovascular accidents that could be interpreted as completed strokes caused by thrombotic occlusion of cerebral arteries or their branches. This was true despite erythrocyte masses that ranged up to three times normal, whether or not the erythrocytosis was compensated and iron replete or decompensated and iron deficient and irrespective of the frequency or degree of hyperviscosity symptoms believed to be related to the cerebral circulation. It has been assumed that a close relation exists between hematocrit levels, cerebral blood flow, and brain injury, and it has also been assumed that lowering the hematocrit level by phlebotomy serves to reduce the risk of cerebral injury, specifically stroke caused by cerebral arterial thrombosis with infarction.[4,5,12–17] These assumptions are given a certain credibility by observations that even a moderate increase in hematocrit level can be associated with a decrease in cerebral blood flow and that a reduction in red cell mass by phlebotomy can increase cerebral blood flow and relieve symptoms believed to be related to hyperviscosity in polycythemia rubra vera and in secondary erythrocytosis.[3–5,25] However, these observations were not made in adults with the erythrocytosis of cyanotic congenital heart disease and cannot be assumed to apply. Whole blood viscosity is a function not only of hematocrit level but also of a number of additional variables including deformability of erythrocytes, aggregation and dispersion of cellular elements, flow velocity (shear rate), temperature, vessel bore, endothelial integrity, and plasma viscosity, of which fibrinogen concentration is an important determinant.[26–28] Blood viscosity may have less effect on flow rates in the microcirculation, in which shear rates are high, a point relevant to the cerebral circulation, in which the arterial supply determining flow consists of vessels of small caliber.[26] Control mechanisms (autoregulation) intrinsic to the normal cerebral circulation may preserve blood flow in the face of hyperviscosity.[26] There is little or no evidence that elevated hematocrit levels in individuals living at high altitudes predispose to stroke.[29] Cerebral thromboses in cyanotic congenital heart disease patients <4 years old express themselves as venous sinus thromboses and are typically associated with iron deficiency (relative anemia in association with hypoxemia).[8–10] Cerebral venous thromboses have not been identified in older patients with cyanotic congenital heart disease whether or not the erythrocytosis is accompanied by iron deficiency.

In contrast to polycythemia rubra vera,[6,7,30,31] the hypoxemia associated with cyanotic congenital heart disease does not result in panmyelosis.[21–23] An increase in formed elements in the latter is confined to red cell mass. Platelet counts are generally in the low range of normal, and leukocyte counts are normal, including granulocytes and basophils, with no increase in leukocyte alkaline phosphatase activity.[21–23] Because the term "polycythemia" refers to an increase in more than one (generally all) of the formed elements in blood (from the Greek *polys*, "many"), the designation is not appropriate for the isolated increase in red cell mass that characterizes the hematologic response in patients with cyanotic congenital heart disease. "Polycythemia" used in that context prompts an erroneous comparison with polycythemia rubra vera. To make the distinction clear, we advise, as have others,[18] that the adaptive increase in red cell mass prompted by the hypoxemia of cyanotic congenital heart disease be designated as "erythrocytosis" rather than "polycythemia."

Cerebrovascular hyperviscosity symptoms in adults with cyanotic congenital heart disease are listed in Table 1. Because these symptoms are sometimes misconstrued as manifestations of transient ischemic attacks and therefore are believed to be antecedents of stroke,[32] the symptoms associated with transient ischemic attacks of carotid or vertebrobasilar distribution are listed in Table 3 for comparison. In this study, there was virtually no overlap. The differences were greater than the similarities. Symptoms or signs of transient ischemic attacks—hemiparesis and/or hemisensory defects, cortical blindness, aphasia, dysarthria, dysphagia, ataxia, or drop attacks—did not occur as manifestations of symptomatic hyperviscosity, nor did the patients manifest any other neurological signs or symptoms. A single exception was the patient who experienced amaurosis fugax. In the population under study, headache, lassitude, dizziness, light-headedness, faintness, altered mentation, a sense of distance or dissociation, visual disturbances (diplopia, blurred vision), numbness, and paresthesia should not be designated as transient ischemic attacks, because none of our patients who experienced those symptoms suffered progressive neurological impairment or a completed stroke (brain infarction) caused by cerebral arterial thrombosis. Hyperviscosity symptoms that might have been construed as transient ischemic attacks did not progress to neurological deficits irrespective of the degree or frequency with which the symptoms recurred and irrespective of the length of follow-up.

The therapeutic use of phlebotomy in patients with cyanotic congenital heart disease has been based on the assumption that the accompanying erythrocytosis predisposes to stroke caused by cerebral arterial thrombosis.[12–17] We call that assumption into question and recommend that the basis for phlebotomy be redefined. Phlebotomy sometimes plays a therapeutic role, but it should not be used to reduce an assumed risk of cerebral arterial thrombosis because, according to our data, that risk did not materialize. The immediate effects of isovolumetric phlebotomy in erythrocytotic adults with cyanotic congenital heart disease are a reduction in whole blood viscosity accompanied by a decrease in peripheral vascular resistance and an increase in stroke volume, systemic blood flow, and systemic arterial oxygen transport.[17,33] Improved pulmonary arterial blood flow and increased pulmonary alveolar oxygen uptake appear to play little or no role in these responses.[34,35] The long-term result of repeated phlebotomy is iron deficiency and microcytosis, which increase whole blood viscosity for a given red cell mass.[8,21] Iron deficiency increases whole blood viscosity because of the greater resistance of microspherocytic red cells to deformation in the microcirculation and because of an increase in the number of microspherocytes.[2,8,36,37] In addition, iron-deficient muscle cells call on anaerobic metabolism for energy needs, leading to

greater lactate production, fatigue, muscle weakness, and impaired exercise performance.[21-23]

Our study was designed to assess the risk of stroke caused by cerebral arterial thrombotic occlusion in adults with cyanotic congenital heart disease. Important but not addressed were potential relations between erythrocytosis, hyperviscosity, and thrombotic occlusive events in other vascular beds. Myocardial infarction has been attributed to hyperviscosity in an occasional erythrocytotic adult.[38,39] Regarding the pulmonary circulation, three observations are relevant: first, Rich's[40] 1948 report of pulmonary vascular obstruction (thrombi) in cyanotic patients with Fallot's tetralogy; second, the tendency for microthrombi to occur in some patients with pulmonary vascular disease (thrombogenic pulmonary arteriopathy)[41]; and third, the uncommon-to-rare occurrence of in situ thrombi in the apexes of the upper lobes of cyanotic patients with pulmonary vascular disease.[21] The efficacy of phlebotomy in these settings has not been tested, but in situ microthrombi in patients with pulmonary vascular disease do not require an increase in red cell mass for their generation.[42] Phlebotomy in patients who are erythrocytotic serves to increase whole blood viscosity by causing iron deficiency and microcytosis (see above), and anticoagulation reinforces intrinsic hemostatic defects in cyanotic congenital heart disease, increasing the risk of hemorrhage.[8,21,23,32]

Because we found no risk of stroke caused by cerebral arterial thrombosis, because the circulatory effects of phlebotomy are transient,[17,33] and because phlebotomy-induced iron deficiency can result in an increase in whole blood viscosity, fatigue, muscle weakness, and impaired exercise performance,[21-23] we do not recommend phlebotomy based on hematocrit level per se. For patients with compensated erythrocytosis, phlebotomy is not recommended even when the hematocrit level reaches or exceeds 70%, as long as symptoms attributed to cerebral hyperviscosity are absent, mild, or moderate.[21,23] Repeated phlebotomy depletes iron stores, induces microcytosis, increases whole blood viscosity, impairs oxygen delivery, increases anaerobic metabolism, and increases lactate production in skeletal muscle.[21-23] In our experience, significant symptomatic hyperviscosity in an iron-replete state seldom occurs with hematocrit levels <65%. When symptoms are present with hematocrit levels <65%, iron deficiency should be suspected. Phlebotomy further depletes iron stores and aggravates rather than alleviates the symptoms, which respond instead to iron repletion.[21-23] When iron is administered therapeutically, the erythrocytotic response should be closely monitored, because the hematocrit level tends to rise rapidly.[21-23] The dose of iron should be small (325 mg of ferrous sulfate or 65 mg of elemental iron once daily). The iron is discontinued at the first discernible rise in hematocrit level, which is usually within a week.[21-23]

The firmest indication for phlebotomy is marked-to-severe symptomatic hyperviscosity in patients with hematocrit levels >65%, provided that dehydration is not the cause. The objective of phlebotomy as herein recommended is the alleviation of intrusive symptoms related to hyperviscosity while minimizing the degree of phlebotomy-induced iron deficiency. The volume of blood withdrawn should be the minimum required to achieve the short-term goal of symptomatic relief.[21-23] What should be avoided is the cycle of phlebotomy-induced iron depletion, treatment with iron followed by an excessive erythrocytotic response, recurrence of hyperviscosity symptoms provoked by excessive erythropoiesis, and additional phlebotomy. Cerebral or noncerebral hyperviscosity symptoms of sufficient severity and persistence to warrant phlebotomy rarely if ever occurred in isolation, i.e., headache alone or myalgias alone (Table 1).

Because a risk of stroke caused by cerebral arterial thrombosis was not established, because the circulatory effects to phlebotomy are transient, and because of the untoward sequelae of iron deficiency, phlebotomy should be reserved for the temporary relief of marked-to-severe hyperviscosity symptoms. Patients should not be phlebotomized according to the hematocrit level per se. Phlebotomy is not justified to reduce an assumed risk of cerebral arterial thrombotic stroke. According to our data, the risk of stroke did not materialize.

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Letter to the Editor

Atrial arrhythmia after Fontan surgery leads to giant thrombus: Opening Pandora's box ☆

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The Fontan procedure is performed in paediatric patients with a single anatomical or functional ventricle aiming to redirect the venous blood flow directly to the lungs bypassing the single ventricle [1]. The most common form of Fontan surgery is the atriopulmonary connection in which the right atrium is connected to the pulmonary artery. In this case, the right atrium functions at higher than normal pressures leading to atrial distension and injury to the sinus node or its blood supply [2]. Late consequence of the above is the occurrence of paroxysmal or persistent atrial arrhythmias [3]. Atrial tachycardias and atrial fibrillation are not uncommon in this population exaggerating the already slow turbulent blood flow inside the right atrium and contributing to the formation of thrombi and increased thromboembolic risk [4].

We report on a 25-year-old man with double inlet left ventricle and Fontan operation (atrio-pulmonary anastomosis) at the age of five years. Although asymptomatic, for several years he had been in sustained atrial flutter that finally degenerated to atrial fibrillation two years ago. When he still was in atrial flutter, a transthoracic echocardiogram had revealed a right atrial (RA) thrombus (Fig. 1A) (Video 1). Anticoagulation with warfarin was initiated but unfortunately due to recurrent gastrointestinal bleeding he was switched to low dose aspirin (37.5–50 mg daily). Cardiac magnetic resonance imaging two years later showed that the thrombus had increased enormously to 100.4 mm × 52.8 mm × 70.0 mm (Fig. 1B) (Video 2). The heterogeneity of the thrombus suggested apposition of several layers of clot as a consequence of the slow blood flow in the right atrium. Despite the dimensions of the thrombus, the flow from the inferior and superior vena cava to the right atrium, as well as the atrio-pulmonary connection and the pulmonary arteries (PA) that lie more posteriorly was unobstructed (Fig. 1C). The localization of the thrombus at the anterior aspect of the dilated right atrium can be appreciated in a left lateral view (Fig. 1D). Despite the size and the age of the thrombus our patient did not have any thromboembolic events.

The formation of an unusually large thrombus in this patient is an extreme sequela of the slow and turbulent blood flow in a dilated right atrium after the Fontan operation in combination with the loss of atrial kick because of long-standing persistent atrial arrhythmias. Even though total cavopulmonary connection is related to lower rates of supraventricular arrhythmias, the thromboembolic risk was found to be similar to the atriopulmonary connection type [5,6]. It is controversial whether patients should be treated with aspirin or anticoagulant drugs after the Fontan surgery, however in the presence of extremely dilated right atrium, atrial arrhythmias or right-to-left shunts chronic anticoagulation treatment is recommended in order to prevent thromboembolic events [6,7].

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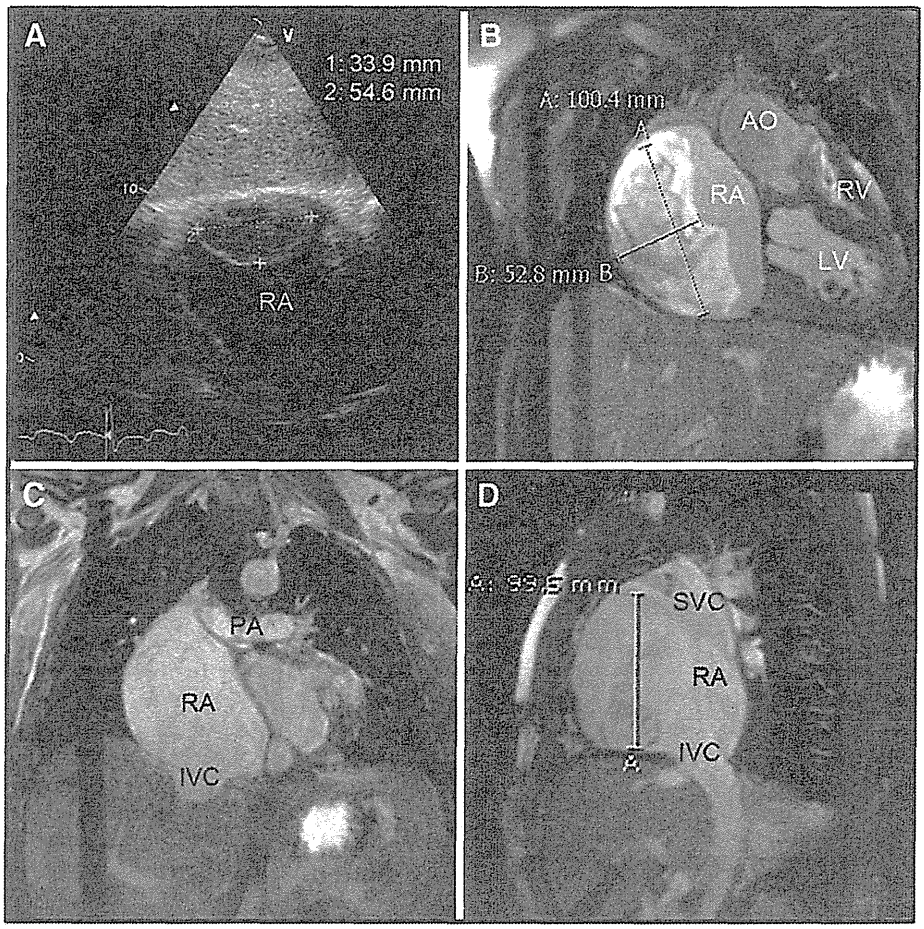

Fig. 1. A thrombus in the right atrium (RA) was present two years ago when the patient was in atrial flutter (echocardiogram shown in 1A) which increased in size enormously after two years that the patient had been in atrial fibrillation (cardiac magnetic resonance 1B to 1D) (see text for details). RA, right atrium; RV, right ventricle; LV, left ventricle; AO, aorta; SVC, superior vena cava; PA, pulmonary artery; IVC, inferior vena cava.

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肝細胞癌との鑑別の困難な multiacinar regenerative nodule を呈した Fontan 術後の 1 剖検例

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An Autopsy Case of Multiple Hepatic Nodules Difficult to Differentiate from Hepatocellular Carcinoma After the Fontan Operation

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報　告

肝細胞癌との鑑別の困難なmultiacinar regenerative noduleを呈したFontan術後の1剖検例

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The Fontan surgery is a type of heart operation used to treat complex congenital heart defects such as a single ventricle. Hepatic complications are commonly reported in patients having undergone Fontan surgery, likely due to hepatic cirrhosis resulting from chronic hepatic congestion caused by the elevated central venous pressure. Here, we describe an autopsy case of multiple hepatic nodules, which developed 16 years after a Fontan surgery in a 20-year-old man. Ultrasound imaging showed multiple isoechoic nodules, clinically resembling hepatocellular carcinoma, in both lobes of the liver, with the largest nodule (>5 cm in diameter) found in the caudate lobe. Pathological findings showed multiple nodular lesions without atypical hepatocytes and severe congestive cirrhosis in the perinodular lesion, and accordingly, we diagnosed the lesion as a regenerative nodule.

The underlying fibrosis and eventual development of cirrhosis increase the risk of developing hepatic nodules or hepatocellular carcinoma. There are many kinds of nodular lesions that resemble hepatocellular carcinoma macroscopically, and both ultrasound and computed tomography findings are useful in characterizing these various types of hepatic nodules. Pathologically, cellular atypia, the size of the nodule, and localization of the portal tract are important factors to take into account when diagnosing hepatic nodules.

Key Words: Fontan surgery, congestive liver cirrhosis, regenerative hepatic lesions

緒　言

Fontan手術は機能心室が1つのみの先天性心疾患に対して行われる上大静脈と下大静脈を肺動脈にバイパスする術式である．近年，Fontan術後の遠隔期の合併症の1つとして肝合併症の報告が増加している[1)~3)]．今回，生前に肝細胞癌が疑われた肝多発結節性病変を呈したFontan術後の1剖検例を経験したので報告する．

症　例

患者：20歳代男性．

主訴：浮腫，腹部膨満感．

家族歴：特記すべき事項なし．

現病歴：出生直後より心雑音があり，1歳時の心臓カテーテル検査において多脾症，完全型心内膜床

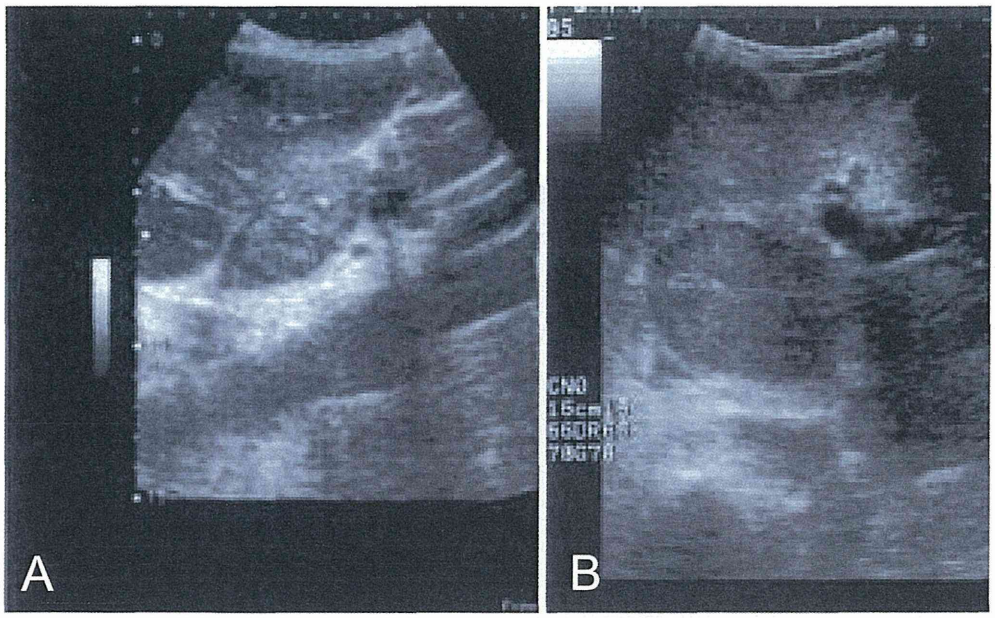

Fig. 1 Ultrasound findings of the hepatic nodule in the caudate lobe
A: The ultrasonogram showed an isoechoic nodule (30 mm in diameter) surrounded by a low echoic area in the caudate lobe.
B: Ultrasound findings 35 months later. The nodule had increased in size to 60 mm in diameter.

欠損，両大血管右室起始，肺動脈狭窄，単一心房，狭小左室，総肺静脈還流異常と診断された．3歳時に右 modified BT shunt を施行したが，5歳時の心臓カテーテル検査で shunt の閉塞が確認された．6歳時，Fontan 手術（total cavopulmonary bypass：TCPC）を施行．術後徐々にチアノーゼの進行がみられ，術後8年目の心臓カテーテル検査において半奇静脈から左肺静脈への動静脈瘻が疑われたため左半奇静脈と左肺静脈の側副血管に対して vascular plug を留置した．入院1年前には左後頭葉の多房性脳膿瘍と診断され，定位的脳膿瘍ドレナージ術により膿瘍は縮小した．また，入院の3年前より6～9ヵ月ごとに腹部超音波検査を施行されており，当初は肝の線維化と肝尾状葉に 30mm 大の占拠性病変が認められていた．その後徐々に両葉にわたって占拠性病変が多発するとともに尾状葉の病変は増大し，最初の超音波施行から2年11ヵ月後に腫瘤は 60mm に達し，肝細胞癌（hepatocellular carcinoma：HCC）も否定できない所見であった（Fig. 1 A，1B）．造影 CT や肝生検などの精査が勧められていたが，腎機能障害や全身状態の不安定さがあるため経過観察となっていた．以後自宅で治療を継続していたが，浮腫，腹部膨満感が増悪し入院となった．

入院時理学所見：体温 35.7℃．血圧　右上肢 90/20mmHg，左上肢 92/22mmHg，右下肢 82mmHg，左下肢 86mmHg．SpO_2 84%．心音にて Levine I～II/VI の汎収縮期雑音を認めた．視線をあわせ，呼びかけに反応はあるものの発語はなし．呼吸音は清．腹部は軟で肝臓を左季肋下に 5cm 触知した．右上肢全体と両下肢に浮腫を認めたが，左上肢には浮腫はみられなかった．

血液生化学検査：入院時検査所見では，血算では赤血球数 $532\times10^4/\mu l$，ヘマトクリット 48.0% と上昇しており，血小板数 $5.0\times10^4/\mu l$ と低下していた．生化学検査では総蛋白 5.6g/dl，アルブミン 3.1g/dl と低下を認め，肝機能は AST 39U/*l*，ALT 26U/*l*，LDH 231U/*l*，総ビリルビン値 3.9mg/dl と AST，LDH の軽度上昇と高ビリルビン血症を認めた．腎機能は尿素窒素 83.0mg/dl，クレアチニン 1.52mg/dl と上昇していたが eGFR は正常であった．電解質検査では，Na 112mEq/*l*，K 5.3mEq/*l*，Cl 78mEq/*l* と低 Na 血症，低 Cl 血症と高 K 血症であった．

入院後経過：入院後電解質の補正を図り，一時的に意識レベルの改善がみられたが徐々に尿量の低下や浮腫の増悪をきたした．種々の薬剤による抗心不全治療を施されたが治療抵抗性で，次第に蘇生への反応にも乏しくなり第21病日に永眠された．

剖検所見：解剖は死後4時間で行われた．腹腔内