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Factors Associated with Stroke Following the Fontan Procedure

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Abstract. We reviewed the results of 68 consecutive Fontan procedures from 1978 to 1993 to determine the frequency of late central neurologic complications of the Fontan procedure in patients living at a mean altitude of 4500 feet. Two surviving patients had transient neurologic symptoms or signs with no corresponding evidence of brain injury by magnetic resonance imaging (MRI), whereas six surviving patients had strokes defined by sustained neurologic symptoms or signs with areas of brain injury identified by MRI [8.8% (6.0–13.0%; 70% confidence limits)]. Collectively, patients with neurologic symptoms had normal hemoglobin values, platelet counts, partial thromboplastin times, and prothrombin times at the onset of clinical neurologic findings. Two patients were taking antiplatelet agents, and one patient was taking warfarin. One of the patients with transient neurologic findings and all of the stroke patients had residual right-to-left shunts. Thus strokes were not uncommon in our patients after the Fontan procedure. Brain injury may result from thromboembolic events associated with residual right-to-left shunts, but our total number of asymptomatic patients with a residual shunt or brain abnormalities by MRI is not known.

Key words: Fontan procedure — Thromboembolic disease — Stroke

Fontan procedures are performed in patients with one effective cardiac ventricle in order to separate the pulmonary and systemic circulations [7]. Systemic venous blood then flows through the lungs without a subpulmonary ventricle. The long-term functional status of patients is related to their pulmonary vascular resistance and ventricular function [3, 6]. Early outcome may be improved by leaving a residual right-to-left atrial shunt in order to maintain cardiac output at the expense of mild to moderate systemic desaturation [2, 5, 10, 12]. Cerebral vascular accidents have been reported as a late postoperative complication of this procedure, although associated factors have not been defined [3, 4, 10, 11, 13–15]. We reviewed the outcome of our Fontan patients to determine the frequency of late-onset central neurologic events and to identify potential predisposing factors for this complication in patients living at moderately high altitude.

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Methods

This study was approved by the Research and Human Subjects Committee of Primary Children's Medical Center. Information was obtained by reviewing each patient's medical record. Between June 1978 and December 1993, a total of 68 patients living at altitudes of 3000–7000 feet (mean 4500 feet) were evaluated at Primary Children's Medical Center and underwent a modified Fontan operation. The mean age at the time of the Fontan operation was 7 years (range 6 months to 15 years). The mean interval of observation since surgery is 4 years (range 7 months to 15 years). There were 39 male patients and 29 female patients. Tricuspid atresia was diagnosed in 18 patients, and 50 patients had other forms of congenital heart disease with single ventricle physiology. In 58 patients the Fontan operation was performed at an altitude of 4800 feet at Primary Children's Medical Center, and 10 patients were referred to institutions near sea level. All referred patients returned to higher elevations after surgery. Three patients have recently moved to altitudes below 1000 feet. The Fontan procedure was performed by a direct atrial-to-pulmonary anastomosis in 40 patients (11 fenestrated), a baffle or conduit total cavopulmonary anastomosis in 20 patients (13 fenestrated), and by incorporating the right ventricle in the atrial-to-pulmonary anastomosis in 8 patients.

Hemodynamic evaluations were performed in all patients preoperatively. A neurologic examination, hematologic studies, and computed tomography (CT) or magnetic resonance imaging (MRI) studies of the brain were performed in all patients with symptoms of potential central nervous system (CNS) injury.

For statistical analysis the measured values are reported as the mean ± standard error. Comparisons of paired and unpaired data were performed with computer-assisted analysis of variance (Stat View II, Abacus Concepts, Berkeley, CA, USA). Significant differences ($p \leq 0.05$) were determined by the Scheffe

Table 1. Clinical profile of patients at the onset of neurologic symptoms

Patient	Hgb (g/dl)	Platelets ($10^3/\mu l$)	PT (sec)	PTT (sec)	O_2 sat. (%)	Postoperative interval	Medications	Neurologic findings
1	15.9	534	14.5	33	93	7 and 8 months[a]	Digoxin	Aphasia, left hemiparesis
2	17.0	348	10.2	26	89	28 months	None	Unsteady gait, left hemiparesis
3	17.2	427	17.5	43	77	2 weeks	Digoxin, diuretics, warfarin	Unsteady gait, right hemiparesis
4	16.9	433	10.9	30	73	5 and 16 months[a]	Digoxin, dipyridamole, aspirin	Right hemiparesis, diplopia, tinnitus
5	15.0	215	14.4	30	88	4 months	Digoxin, diuretics, captopril, amoxicillin	Diplopia, ataxia, facial palsy
6	15.0	418	13.7	30	95	6 months	Aspirin	Slurred speech, right hemiparesis
7	13.9	317	13.6	35	90	19 months	Digoxin, diuretics	Seizure, right hemiparesis
8	15.4	222	12.1	36	81	41 months	Digoxin, amoxicillin	Left hemiparesis

Hgb, hemoglobin; PT, prothrombin time; PTT, partial thromboplastin time.
[a] Separate recurrent episodes.

F-test. A chi-square test was used to determine if several preoperative factors influenced neurologic outcome.

Results

No patients manifested neurologic symptoms prior to discharge from the hospital after surgery. Eight patients later developed acute symptoms consistent with central neurologic injury. The clinical profile of each patient at the onset of neurologic symptoms is outlined in Table 1. Patients 1 and 4 had recurrent episodes of neurologic symptoms. Patients had normal values of hemoglobin (15.8 ± 0.4 g/dl), platelet count (364 ± 39 $10^3/\mu l$), and partial thromboplastin time (32.9 ± 1.8 seconds). Prothrombin times were normal in all but one patient, who was started and maintained on warfarin early after surgery. Three patients were clinically cyanotic. The other patients were minimally desaturated for this altitude because coronary sinus blood mixed with pulmonary venous return in each case except for patient 1. Symptoms developed as early as 2 weeks and as late as 41 months after surgery. Two patients were on aspirin, and one of these patients was also on dipyridamole. All patients were predominantly in sinus rhythm; however, three patients had documented periods of junctional or atrial arrhythmias during 24-hour monitoring. Bleeding times and other coagulation studies were not performed in all patients. However, patient 1 had a mildly decreased protein C value of 50% (60–150%), and patient 5 had a mildly decreased protein S value of 51% (56–180%). There was no history of strokes at a young age in relatives of the eight affected patients. CT scans were performed in five patients. A summary of findings by CT and MRI is given in Table 2. The MRI scans of patient 3 are shown in Figures 1 and 2. The chronic infarct in patient 8 may have occurred at the time of a previous palliative operation that was complicated by a neurologic injury. Transthoracic echocardiograms identified a potential right atrial thrombus in only one patient.

The onset of neurologic symptoms occurred at the patient's home altitude (4400–6500 feet) in all but one patient. Patient 7 experienced a stroke while vacationing at sea level. Four patients developed symptoms at rest, and four patients developed symptoms during nonstrenuous physical activity. With anticoagulation and extended observation, neurologic symptoms and signs have been alleviated or resolved in all of these patients.

The type of congenital heart anomaly was not a significant factor in the development of neurologic symptoms. Patients 1 and 3 had tricuspid atresia; patients 2, 5, and 7 had S, L, L-double-inlet single ventricle; and patients 4, 6, and 8 had complex atrioventricular septal defects with single ventricle physiology. The type of Fontan procedure also did not significantly influence neurologic outcome. In four patients a conduit or baffle was used to create a total cavopulmonary anastomosis, and in four pa-

Table 2. Results of computed tomography and magnetic resonance imaging studies

Patient	Computed tomography	Abnormalities by magnetic resonance imaging				
		Acute/subacute	Chronic	White matter	Atrophy	Angiography
1	Normal	None	None	None	Minimal	Normal
2	ND	Right cerebellum: 1 cm infarct	Occiput: bilateral 1 cm infarcts	Bright punctate and patchy foci: left > right	Mild	ND
3	Right basal ganglion infarct	Brainstem and left cerebellum: 5- to 6-mm bright foci	Right basal ganglion: 1- to 2-cm infarct	None	Mild	Slow flow or occlusion of distal basilar artery
4	Normal	None	Right caudate nucleus: small infarct	Several small right punctate foci	None	ND
5	Brainstem infarct	Right brainstem and cerebellum: 2- to 3-cm infarct	None	None	None	ND
6	Left middle cerebral artery infarct	Left basal ganglion: parietal and temporal large infarct	None	None	None	Normal
7	ND	Left temporal and parietal ischemia, resolved within 6 days	Right cerebellum: 1 cm infarct	Five punctate bright foci	None	ND
8	ND	None	Right occiput: 1- to 2-cm infarct	Right hemisphere: 8-mm bright focus	Mild to moderate	ND

All studies were performed at the onset of neurologic symptoms, except for the MRI scan of patient 4, which was performed 3 years thereafter.
ND, not done.

tients a direct atrial-to-pulmonary artery anastomosis was used. Patients 3 and 6 had 4.0 mm fenestrations left at the time of surgery. These fenestrations were closed with 17 mm clamshell occlusion devices (USCI Angiographics, Tewksbury, MA, USA). Patient 3 developed symptoms before the fenestration was closed, and patient 6 developed symptoms 14 weeks after the fenestration was closed. At the onset of neurologic symptoms, only patient 1 had no angiographic or echocardiographic evidence of a residual right-to-left shunt secondary to a fenestration, a baffle leak, or a systemic venous collateral vessel that communicated with the pulmonary venous atrium. Figure 3 demonstrates one of the systemic venous collaterals identified in patient 4. By chi-square analysis, the presence of a surgical fenestration was not associated with a significantly different frequency of neurologic symptoms or stroke.

Table 3 lists the preoperative and postoperative hemodynamic measurements of patients who developed neurologic symptoms and other patients who survived the early postoperative period. Among the 68 Fontan patients there were four early deaths prior to discharge after surgery. The transpulmonary gradients were significantly greater in patients who developed neurologic symptoms, although, there were no differences in calculated values of pulmonary vascular resistance. Patients with and without subsequent neurologic symptoms also had similar systemic venous pressures during the early postoperative period. Of 31 patients with a preoperative mean pulmonary arterial pressure (MPAP) $\geq$15 mmHg, eight ultimately died ($p < 0.05$): 2 of

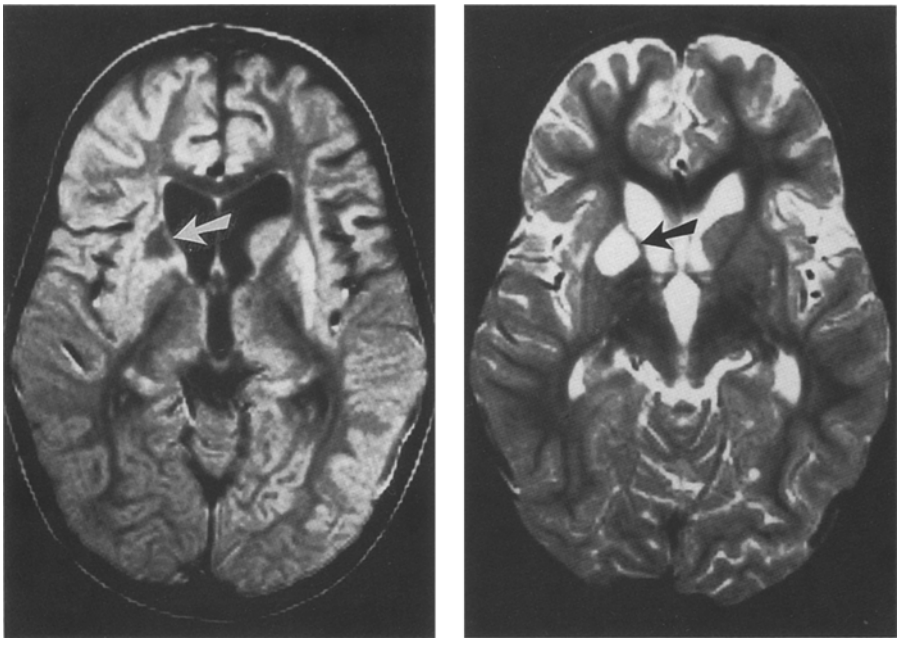

Fig. 1. Magnetic resonance images of patient 3. Axial proton density **(left)** and T2-weighted **(right)** magnetic resonance images at two scan levels through the basal ganglia demonstrate a 2 cm area of focal porencephaly (infarction) in the right corpus striatum (*arrows*) associated with atrophy of the head of the caudate nucleus. The lateral and third ventricles are enlarged, consistent with mild global atrophy.

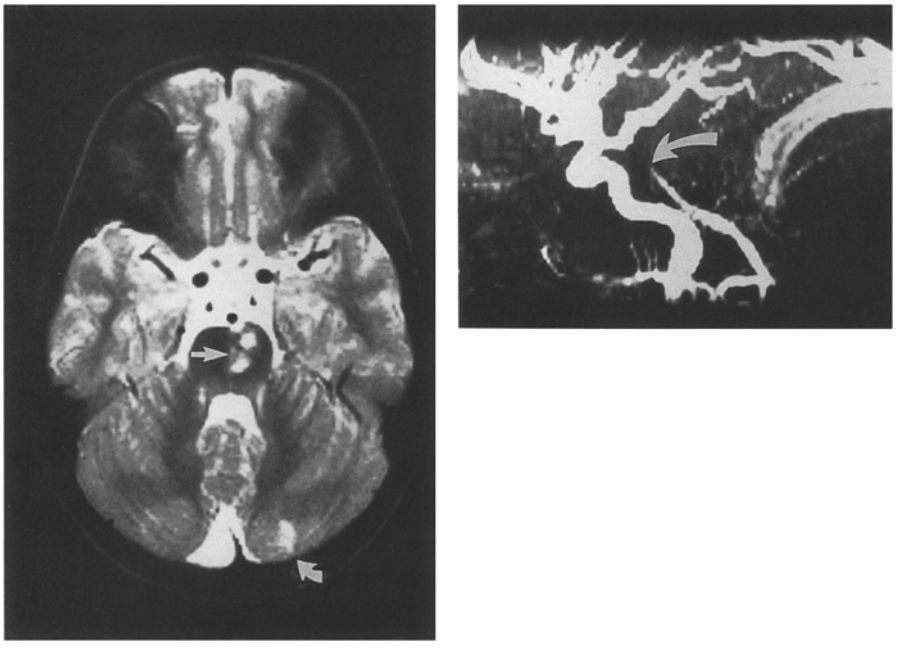

Fig. 2. Magnetic resonance imaging and angiography of patient 3. **(Left)** Axial T2-weighted image at the level of the pons demonstrates two 5- to 6-mm foci of bright signal in the pons (*straight arrow*) and a single bright focus in the left cerebellar hemisphere (*curved arrow*). The findings are consistent with focal areas of infarction in the distribution of the posterior circulation that are a potential result of multiple emboli. **(Right)** Lateral maximum intensity projection magnetic resonance angiogram based on a three-dimensional time-of-flight acquisition. The absence of signal in the distal basilar artery (*arrow*) indicates either occlusion or slow flow, probably related to the same process causing the abnormalities seen in the brainstem and cerebellum. Note the normal flow in the carotid arteries and their intracranial branches.

the 23 surviving patients with a preoperative MPAP $\geq$15 mmHg and 4 of the 32 surviving patients with a preoperative MPAP $<$ 15 mmHg had a stroke ($p >$ 0.05). None of the late deaths were thought to be related to a stroke.

Seven of the eight patients with neurologic symptoms and 35 of the other 56 patients who survived the early postoperative period were studied by heart catheterization after surgery. One of the eight symptomatic patients had no angiographic evidence of a right-to-left shunt, and one had evidence of a right-to-left shunt by echocardiography and has

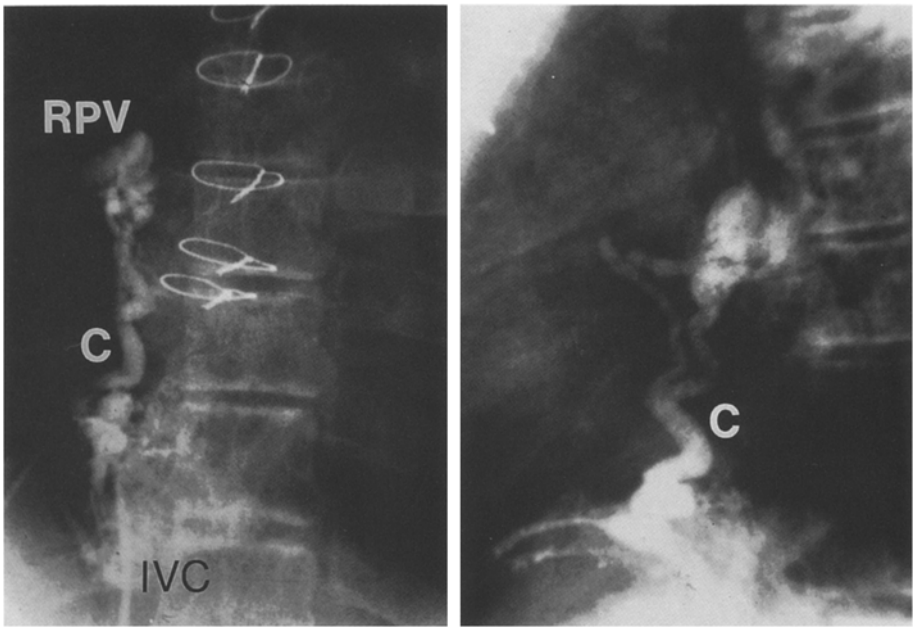

Fig. 3. Selective manual injection of contrast in a systemic venous collateral in patient 4. A tortuous collateral (*C*) arises from the inferior vena cava (*IVC*) and branches into several smaller vessels before draining with the right pulmonary veins (*RPV*) into the pulmonary venous atrium.

Table 3. Preoperative and postoperative hemodynamic measurements during heart catheterization

Measurement	Patients with neurologic symptoms		Patients without neurologic symptoms	
	Preop. (n = 8)	Postop. (n = 7)	Preop. (n = 56)	Postop. (n = 35)
Hgb (g/dl)	17.8 ± 0.6	16.3 ± 0.9	18.5 ± 0.3	15.9 ± 0.3**
O_2 sat. (%)	81.3 ± 1.8	85.0 ± 2.1	77.8 ± 1.0	88.3 ± 1.1**
VEDP (mmHg)	6.6 ± 1.0	7.4 ± 1.2	7.8 ± 0.4	7.5 ± 0.5
MPAP (mmHg)	15.5 ± 1.9	12.4 ± 0.8	13.9 ± 0.5	12.8 ± 0.7**
ΔP (mmHg)	10.9 ± 2.1*	5.3 ± 0.8***	7.2 ± 0.4	5.8 ± 0.4**
PVR (units-m^2)	2.5 ± 0.4	2.7 ± 0.6	2.7 ± 0.2	2.5 ± 0.2
Postoperative interval (months)	—	52 ± 17	—	40 ± 6

Results are given as the mean ± SE.

* $p < 0.05$: Comparison of preoperative values for patients with and without neurologic symptoms.

** $p < 0.05$: Comparison of preoperative and postoperative values for patients without neurologic symptoms.

*** $p < 0.05$: Comparison of preoperative and postoperative values for patients with neurologic symptoms.

Hgb, hemoglobin; MPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; O_2 sat, systemic oxygen saturation; ΔP, transpulmonary gradient; VEDP, ventricular end-diastolic pressure.

not undergone postoperative heart catheterization. When patients with surgical fenestrations were excluded, a residual right-to-left shunt was identified by angiography or echocardiography in six of seven patients with neurologic symptoms and only 3 of 21 asymptomatic patients who have undergone postoperative heart catheterization ($p < 0.005$). Some patients with surgical fenestrations have additional sites of right-to-left shunt. Twenty patients without neurologic symptoms have not had invasive studies to exclude potential right-to-left shunts. An old infarct was identified in one patient during an MRI evaluation for chronic headaches; there was no history of focal neurologic symptoms.

Discussion

In this retrospective study, we identified 8 of 68 consecutive Fontan patients who experienced late central neurologic symptoms. Six of these patients had a stroke [8.8% (6.0–13.0%, 70% confidence limits)]. Seven of the eight patients had a documented right-to-left shunt, and four of these patients had

additional abnormalities, seen by MRI, consistent with old infarcts. We have not identified a mechanism for neurologic symptoms other than a residual right-to-left shunt and potential thromboembolic disease.

In children strokes are often associated with congenital heart disease and have also been reported following the Fontan procedure [1, 4, 6, 11, 13–15]. The frequency of strokes was relatively high in our patient population. It is unlikely that surgical technique influenced the risk of this complication, as Fontan procedures were performed at institutions near sea level in two of the affected patients. Coagulation factor abnormalities have been detected in Fontan patients [4]. We did not evaluate specific coagulation factors in all patients; however, the importance of minor laboratory abnormalities in the pathogenesis of strokes in Fontan patients warrants further investigation. Fontan patients may be vulnerable to thrombus formation as a result of decreased cardiac output. In our patients, cardiac output may be further impaired by varying degrees of alveolar hypoxia and increased pulmonary vascular resistance at higher elevations [9].

Our MRI images are consistent with brain injury secondary to thromboembolic events. Lesions were suggestive of infarcts in arterial distributions, and watershed regions were spared. In some patients there were acute and chronic lesions. Symptoms did not uniformly correlate with areas of brain injury detected by MRI. Future Fontan candidates must be studied prospectively to determine the degree of subclinical brain injury that occurs before and after the Fontan procedure. Using transesophageal echocardiography, Fyfe and associates have identified thrombus formation at cavopulmonary anastomoses in Fontan patients [8]. We now have probes of appropriate size and may be able to determine if late neurologic symptoms are associated with detectable thrombi in future patients.

Early outcome of the Fontan procedure may be improved by leaving a residual fenestration, although our results suggest that a residual right-to-left shunt may increase a patient's risk for stroke. Unfortunately, we do not know the number of asymptomatic patients with a residual shunt. Many patients with small shunts are not clinically cyanotic. Baffle leaks and surgical fenestrations may be closed with transcatheter devices. However, some patients may develop late right-to-left shunts through complex systemic venous collaterals that cannot be completely eliminated by coil or device embolization or surgery.

Some physicians have empirically treated Fontan patients with antiplatelet agents or warfarin to prevent thrombus formation. Two of our patients were taking antiplatelet agents, and one patient had a reasonable therapeutic effect from warfarin. It is possible that some thromboembolic events cannot be prevented by these agents; or, alternatively, strokes may be mediated by a different mechanism. A randomized prospective multicenter study may be needed to determine the relevance of coagulation factor abnormalities and the efficacy of antiplatelet agents and anticoagulants in preventing strokes in patients after the Fontan procedure.

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