Original Article
⟨Clinical Science: Congenital Heart Disease⟩

Thrombotic or Bleeding Complications in Patients Undergoing the Fontan Procedure and Receiving Prophylactic Anticoagulation and/or Antiplatelet Therapy

Yuji Tanaka, MD, PhD

Department of Pediatrics, National Hospital Organization Kagoshima Medical Center, Kagoshima, Japan

Background: Although many patients undergoing the Fontan procedure require anticoagulants or antiplatelet drugs, there is no consensus regarding thromboprophylaxis after this procedure.

Methods: To clarify the incidence of thrombotic or bleeding complications and their characteristics, we retrospectively studied 49 patients (34 male and 15 female) who underwent the Fontan procedure between 1989 and 2012. Their average age was 16.3 ± 7.7 years, the average age at which total cavopulmonary connection surgery was performed was 4.5 ± 3.7 years, and the mean duration of postoperative observation was 59.1 ± 45 months.

Results: All patients received warfarin and all but one received aspirin. Three patients developed cerebral infarction, one of whom also developed renal infarction. With prompt treatment, all three patients recovered without sequelae. With regard to bleeding complications, one of three patients who developed pulmonary hemorrhage died. Gastrointestinal bleeding occurred on six occasions in three patients, only one of whom had associated abdominal pain. Urgent blood transfusions were necessary on five of these occasions. Additionally, subcutaneous hemorrhage, macrohematuria, ovarian hemorrhage, and polyhypermenorrhea also occurred. In patients with bleeding complications, the mean prothrombin time/international normalized ratio was 1.9 ± 0.5. These hemorrhagic events were managed by the discontinuation of aspirin and reduction of the warfarin dosage.

Conclusion: It is necessary to determine whether a combination of aspirin and warfarin is indicated for maintaining adequate circulation after the Fontan procedure. Because combination treatments are likely to cause more bleeding complications, the use of individual drugs should be investigated.

Keywords: Fontan, thromboprophylaxis, anticoagulation, antiplatelet, bleeding ulcer

Introduction

The Fontan procedure has been established in pediatric cardiac surgery, and the number of patients reaching adulthood having successfully undergone this procedure is increasing. While prognosis with the Fontan procedure is considered to be good, the three major causes of death have been reported to be thromboembolism (TE), heart failure, and sudden death.[1]

Till date, antiplatelet therapy has been used to prevent arterial thrombosis assumed to be caused by arteriosclerosis, and anticoagulant therapy has been used to prevent venous thrombosis. There are no criteria, however, for drug use in patients who have undergone the Fontan procedure. In atrial fibrillation, commonly caused by venous thrombosis, inflammatory changes in the atrial wall due to the loss of regular contraction and relaxation is recognized as an underlying mechanism leading to thrombus formation.[2] Following the Fontan procedure when the pulsatile flow is attenuated, the Fontan circulation is in a hypercoagulable state.[3] Furthermore, while the relative merits and demerits of aspirin and warfarin in the prevention of TE have been discussed, both drugs remain to be controversial and have been reported to be

inadequate.[4, 5)]

It has long been thought that even microthrombi could have adverse effects on the pulmonary vascular bed. Thus, in our department, warfarin and aspirin are generally used in combination following the Glenn operation. However, with the increasing number of adult patients, the incidence of complications are also increased.

Therefore, to ascertain the state of anticoagulant and antiplatelet therapies, we retrospectively examined the characteristics of patients who suffered infarction and hemorrhagic events during outpatient follow-ups.

Subjects and Methods

The study included 49 patients who had undergone total cavopulmonary connection (TCPC) and who were followed up on an outpatient basis in our department between 1998 and 2012. All patients underwent surgery and cardiac catheterization at nonprefectural institutions.

There were 34 male and 15 female patients, with a mean age of 16.3 ± 7.7 years (5–39 years), mean age at TCPC surgery of 4.5 ± 3.7 years (2–25 years), and mean postoperative follow-up period of 59.1 ± 45 months (31–310 months). The surgical procedure was ex-TCPC in 36 patients (Björk→TCPC conversion in one patient), Lt-TCPC in 10, intra-atrial conduit in two, and atriopulmonary connection in one. The underlying disease was asplenia in 10 patients; tricuspid atresia (TA; including severe tricuspid stenosis) in 10; double-outlet right ventricle in nine; mitral atresia in six; hypoplastic left heart syndrome (HLHS) in four; Ebstein's anomaly, double-outlet left ventricle, and pulmonary atresia with intact ventricular septum (PA-IVS) in two each; and polysplenia, crisscross heart, transposition of the great arteries type III, and complete atrioventricular septal defect in one each. Furthermore, complications included pulmonary arteriovenous fistula in one patient and residual pulmonary artery stump in 12. Five patients had mechanical valves.

In the postoperative anticoagulant therapy, after completion of the Glenn operation, warfarin was initiated to achieve a prothrombin time–international normalized ratio (PT-INR) of 1.6–2.2 or PT-INR of 2.5 for patients with a mechanical valve, and as a general rule, low-dose aspirin (1–2 mg/kg/day, with enteric tablets used for adults) was used in combination with an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin II receptor blocker (ARB) to protect the myocardium.

Following discharge, blood was sampled to monitor warfarin control on regular outpatient visits every 1–2 months, and transthoracic echography (TTE) was performed every 3–6 months. In the present study, we retrospectively examined the presence or absence of infarction and hemorrhage-related events.

Results

1. Oral Medication before Events

Warfarin was administered to 49 patients (100%), aspirin to 48 (98%), ACE-I to 16 (33%), ARB to 30 (61%), β blocker to 15 (31%), aldosterone blocker to 11 (22%), and bosentan to 5 (10%).

2. Infarction Cases (Table 1)

Cerebral infarction was observed in three of 49 patients (6%). The age at onset in these three patients was 35, 26, and 15 years, and on routine examination before the onset, thrombi were not detected. In case 1 with underlying pulmonary arteriovenous fistula, aspirin was discontinued because of severe hypermenorrhea and warfarin was also subsequently withdrawn, during which time cerebral infarction occurred. At the time of the onset of cerebral infarction, PT-INR was 1.28 and the D-dimer level was 0.13. In case 2, who responded to warfarin monotherapy with a PT-INR of 2.13, paralysis developed, and TTE and transesophageal echography

Table 1 Characteristics of patients with cerebral infarction

Case	Age of onset (years)	Years after Fontan procedure (years)	Surgical procedure	Diagnosis	Risk factors for thromboembolism	Drugs	PT-INR
1	35	18	Ex-TCPC (TCPC conversion)	TA1b	Pulmonary arterio-venous fistula	W + A interrupted	1.28
2	26	18	Lt-TCPC	DORV	Pulmonary blind pouch	W	2.13
3	15	5	Ex-TCPC	Asplenia	Artificial valve	W + A	1.80

A, aspirin; DORV, double outlet right ventricle; Ex, extra-cardiac conduit; Lt, lateral tunnel; TCPC, total cavo-pulmonary connection; TA, tricuspid atresia; W: warfarin.
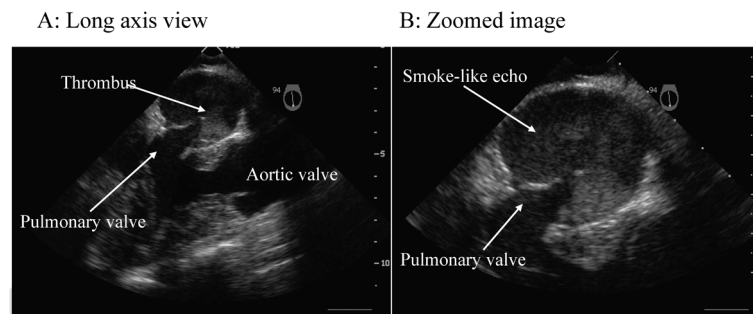
A: Long axis view   B: Zoomed image

Fig. 1 Transesophageal echocardiography findings in a patient with cerebral infarction from a thrombus in a blind intracardiac pouch

Table 2 Characteristics of patients with gastrointestinal hemorrhage

Case	Age (years)	Chief complaint	PT-INR	Pre Hb	Post Hb	Aspirin	*H. pylori*	Blood transfusion	Emergency endoscopy
1-①	6	Common cold, fever	1.77	10.7	5.4	1.8 mg/kg/day	Not examined	+	Not done
1-②	7	Pale face	1.66	10.5	6.1	1 mg/kg/day	Not examined	+	Not done
1-③	8	Fatigue	1.82	13.7	8.9	1 mg/kg/day	Positive	−	Not done
1-④	15	Pallor	3.50	15.0	9.4	Enteric-coated aspirin 100 mg/alternate-day	Negative (after pylorus eradication)	+	Bleeding ulcer
2	19	Fatigue	2.74	15.8	7.7	Enteric-coated aspirin 100 mg/alternate-day	Negative	+	Bleeding ulcer
3	9	Abdominal pain	2.23	12.7	4.7	1.25 mg/kg/day	Negative	+	Bleeding ulcer

1-①–④ denote four episodes in the same patient.

(TEE) revealed a thrombus in the blind intracardiac pouch stump with a smoke-like echo (Fig. 1). Following hospitalization, heparin and brain-preservation therapy was initiated, and with concurrent aspirin, the subject recovered from the cerebral infarction. However, during follow-up, renal infarction occurred; therefore, after increasing the warfarin dose, surgery was performed for pulmonary atresia. Case 3 was a patient who had undergone atrioventricular valve replacement, and while receiving oral warfarin and aspirin therapy, paralysis and anarthria occurred when PT-INR was low at 1.80. TEE revealed intra-arterial mural thrombus with a smoke-like echo.

Fortunately, all patients were admitted to the Department of Neurology, where the symptoms were alleviated with thrombolytic therapy and without any sequelae.

3. Hemorrhage Cases

No cases of cerebral hemorrhage were observed.

Gastrointestinal bleeding was observed in three patients (Table 2).

Three patients exhibited a total of six events of gastrointestinal bleeding. Only one of these three patients complained of abdominal pain. Five hemorrhagic events required emergency transfusion, and all patients were receiving oral warfarin and aspirin therapy. Events 1–4 occurred in the same patient (asplenia). The site of the hemorrhage could not be diagnosed using lower gastrointestinal contrast-enhanced endoscopy and Meckel diverticulum scintigraphy performed at the time of events 1 and 2 and using endoscopy performed several days later. At the time of event 3, urine was clearly positive for Helicobacter pylori antigens, and bacterial elimination was unsuccessful. Therefore, aspirin was discontinued because of the risk of ulceration. When the patient was 13 years old, H. pylori was successfully eliminated with the combined use of metronidazole, and alternate-day administration of enteric-coated aspirin tablets was recommended. However, at 15 years of age, the subject underwent atrioventricular valve replacement, and ulceration recurred 2 months later (case 1, event 4). At this point, emergency endoscopy following blood transfusion revealed the adhesion of a blood clot
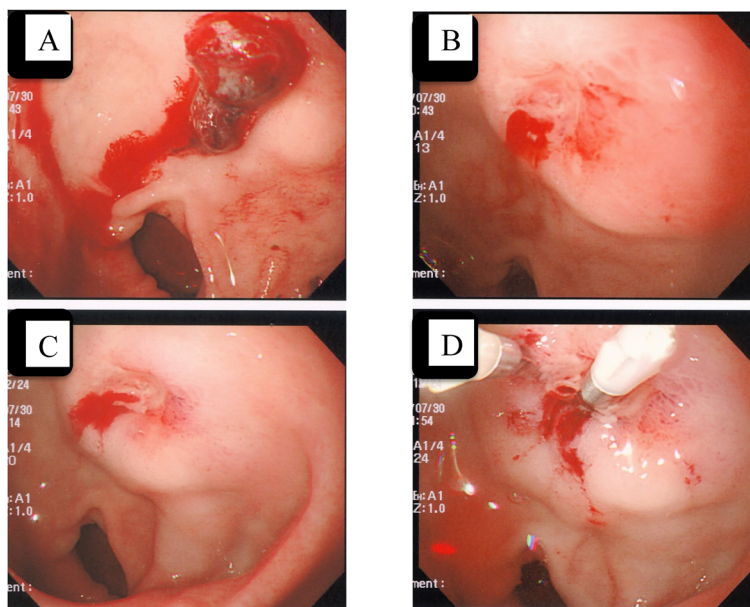
Fig. 2 A case of duodenal ulcer treated successfully by endoscopic clipping
A: Adherent blood clot. B: Spurting bleed from the exposed vessel. C: Local injection of hypertonic saline–epinephrine.
D: Clipping of the responsible vessel.

to the posterior wall of the duodenal bulb, below which a superficial ulceration of approximately 3 mm and an exposed vessel with arterial bleeding were confirmed. As bleeding could not be completely stopped with a hypertonic saline injection, hemostasis was implemented with clipping (Fig. 2). Case 2 was a 19-year-old male (PA-IVS with sinusoidal communication, old myocardial infarction, and occlusion of the left anterior descending coronary artery) who noticed blackish feces several days earlier with no abdominal pain. As examination revealed the subject to be in a pre-shock state and pale, he was hospitalized. Case 3 was a 9-year-old boy (TAIIc and CoA) who was conscious, oriented, and alert and the only patient to complain of abdominal pain, for which he consulted a local pediatrician. However, abdominal echography revealed no abnormality, and constipation was diagnosed. An enema was given, and his condition was monitored. He went into a state of pre-shock 5 days later. Despite instructing his mother to pay frequent attention to whether any blackish feces appeared, she did not observe any.

Apart from case 1, event 3, for all patients, emergency transfusion was required, and after discontinuing warfarin and aspirin, menatetrenone was administered and the combined use of proton-pump inhibitors (PPI) was initiated. Thereafter, once in a stable condition, warfarin alone was recommended in all patients while continuing PPI therapy. However, only in case 2, coronary sequelae were observed. Thus, on the following day, enteric-coated aspirin tablets were recommended on alternate days.

Pulmonary Hemorrhage Occurred in Three Patients

A 27-year-old male with asplenia and a history of atriopulmonary connection surgery died of critical pulmonary hemorrhage 14 years after undergoing the Fontan procedure. As the patient had long exhibited bloody sputum, cardiac catheterization was recommended. However, following previous cardiac catheterization contrast-enhanced imaging, macroscopic hematuria was observed, but the patient had refused to undergo cardiac catheterization for 10 years. During oral warfarin and aspirin therapy, although PT-INR at hospitalization was relatively low at 1.48, massive bleeding occurred suddenly and the patient's life could not be saved. The presence or absence of abnormal collateral vessels was unclear as they were not investigated on computed tomography (CT) or echography, and consent was not obtained for pathologic autopsy.

A 19-year-old male with MA and a history of atrioventricular valve replacement surgery suffered from diffuse alveolar hemorrhage 16 years after undergoing the Fontan procedure (Fig. 3-A). Even after coil embolization of the collateral vessels, hemoptysis repeatedly

occurred, which resolved upon the discontinuation of aspirin. Therefore, despite the artificial valve, the warfarin dosage had to be temporarily reduced. The Department of Respiratory Medicine was consulted, and continuous low-dose clarithromycin therapy alleviated the hemoptysis attacks.

The aforementioned 38-year-old female with a history of cerebral infarction (TAIb) was being treated with warfarin alone. However, during a routine health check-up 3 years after the cerebral infarction, an infiltrative shadow was identified in the left lung, and pneumonia was initially suspected. However, the shadow gradually grew and pulmonary hemorrhage was diagnosed by CT (Fig. 3-B). PT-INR at diagnosis was 2.29. Therefore, the warfarin dosage was temporarily reduced, and the hemorrhage resolved without any recurrence of cerebral infarction.

Other Cases (Some Patients with Multiple Symptoms)

Severe subcutaneous bleeding occurred in four patients. Two patients had frequent nose bleeds, severe hypermenorrhea, and repeated epigastric pain. One patient had macroscopic hematuria, ovarian bleeding, aspirin-induced rash, and hepatopathy.

All patients were successfully treated by discontinuation of aspirin, reduction of warfarin dose, and administration of hemostatic drugs. Furthermore, some patients with cuts and contusions required some time for hemostasis to occur but could be treated by covering/sealing with an alginate dressing and without changing the oral therapy.

In patients with a mean PT-INR of 1.9 ± 0.5 (1.47–2.31) at the time of a hemorrhagic event and who were receiving warfarin combined with aspirin, the hemorrhagic event occurred irrespective of PT-INR. A high
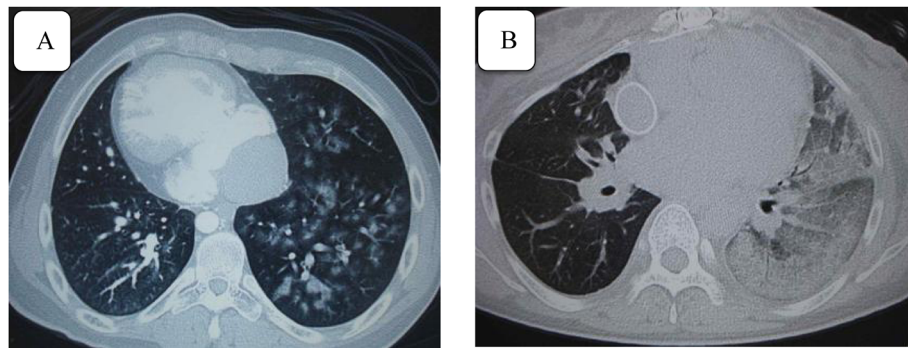

Fig. 3 Thoracic computed tomography (CT) findings
A: 19-year-old man. Enhanced CT image shows diffuse alveolar hemorrhage. B: 38-year-old woman. Plain CT image shows left pulmonary hemorrhage.
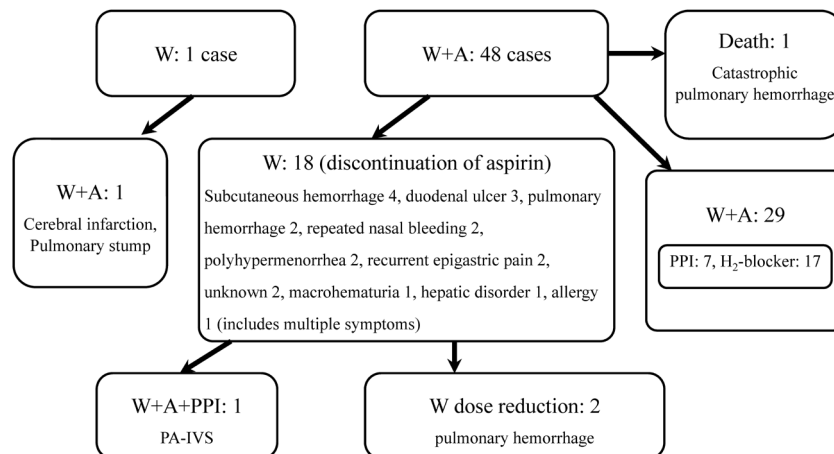

Fig. 4 Changes in medication of patients after Fontan procedure
A, aspirin; PPI, proton pump inhibitor; PA-IVS, pulmonary atresia-intact ventricular septum; W, warfarin.

PT-INR did not imply bleeding, and routine blood sampling conducted 1 week after vomiting and diarrhea revealed that although some patients showed a temporarily elevated PT-INR of up to 10.5, fortunately no hemorrhagic event occurred.

4. Changes in Medication Following an Event (Fig. 4)

In patients with a residual blind intracardiac pouch pulmonary artery stump who suffered cerebral infarction, warfarin and aspirin therapy was initiated. In 18 patients, including those with pulmonary hemorrhage and gastrointestinal bleeding, aspirin was discontinued and warfarin monotherapy was started. Two patients with pulmonary hemorrhage required a temporary warfarin dose reduction, and aspirin was recommended only for the PA-IVS patient with a coronary lesion upon administration of PPI. Furthermore, in the 29 patients receiving both agents, prophylactic PPI or H2 blockers were initiated regardless of the presence or absence of ulceration. Following the initiation of antiulcer agents, no patient suffered from gastrointestinal bleeding.

Discussion

Among the adult patients who undergo the Fontan procedure, approximately 17% (one in every six patients) have silent pulmonary emboli, which have not been observed in patients receiving warfarin therapy.[3] At the same time, if silent emboli gradually increase pulmonary vascular resistance, then anticoagulant therapy might improve the long-term functioning of Fontan circulation, thereby improving survival. When the blood flow velocity becomes slow, red blood cells form a rouleaux and increase shear stress, thereby causing the von Willebrand factor (vWF) to change and cause increased thrombotic tendency.[2] However, in normal laminar flow, it is unclear how vascular endothelial cells with antithrombotic function change in the Fontan circulation and how polycytemia and a congested liver affect liver-derived clotting factors.

According to a report on adult atrial fibrillation, compared to the clopidogrel and aspirin combination therapy group, the warfarin monotherapy group exhibited a greater event-prevention effect.[6] Although fibrin thrombi anticoagulant therapy is considered to be superior to the antiplatelet therapy, for the treatment of Fontan venous thrombosis, warfarin and aspirin are comparable.

According to the 2011 report from the Fontan Anticoagulation Study Group by Monagle et al.,[4] a 2-year multicenter prospective controlled study of warfarin and aspirin for the primary prevention of TE following the Fontan procedure revealed no difference between the two groups, and the preventive effect itself in the two groups was therefore considered inadequate. Thus, it is concluded that to prevent TE in the long-term, future studies should examine unlimited factor Xa inhibitors, novel oral anticoagulants (NOAC) used in combination with warfarin and aspirin, and the intensification of antiplatelet agents. In future clinical trials, to determine whether microvascular TE has an adverse effect on pulmonary and systemic circulations, the need for regular TEE has been proposed. In the secondary analysis of the same trial, McCrindle et al.[5] reported that at 2.5 years following surgery, 31% of the patients exhibited thrombosis, with no difference observed between the warfarin and aspirin and the warfarin-poor control groups (PT-INR＜2.0); in contrast, thrombosis was more common. However, on the other hand, as all thrombi were venous, it is concluded that NOAC must be examined in the future.

Manlhiot et al.[7] reported that TE prevention is needed during the period following the initial palliative surgery in patients with a single ventricle and Glenn's operation, as well as the Fontan procedure. They also reported that enoxaparin and low-molecular-weight heparin exhibit a preventive effect following the initial palliative surgery and the Glenn operation, whereas following the Fontan procedure, the preventive effect in the warfarin group was superior to that in the aspirin and nontreated groups, with no difference in the hemorrhagic complications.

In contrast, Uno et al.[8] measured thrombin–antithrombin-3 complex and α2-plasmin inhibitor–plasmin complex levels in a 16-year-old child following the Fontan procedure. Because both levels had normalized at 12 months postoperatively, they proposed administering warfarin for 1 year postoperatively, then subsequently changing to antiplatelet therapy. Ohuchi et al.[9] examined patients who were administered warfarin in combination with aspirin following the Fontan procedure and reported that hemorrhagic complications arose early and that TE commonly developed within 6 months and 15 years postoperatively. Thus, in low-risk

patients, warfarin should be discontinued at 1 year after the Fontan procedure to reduce hemorrhagic complications. However, in 7% of the patients, warfarin was recommenced, and it has been indicated that as PT-INR was not examined, it is difficult to standardize the anticoagulant therapy.

According to Hallas et al.,[10] in recent years, adults with atrial fibrillation are increasingly being administered several antiplatelet agents and anticoagulants in combination, and in a study of gastrointestinal bleeding, it was reported that when the adjusted odd ratios for aspirin monotherapy and warfarin monotherapy were 1.8, respectively, the corresponding odds ratios for combined use were 5.3. Thus, the need for ulcer prevention in combination therapy is considered more and more important. Furthermore, in the Hokusai-VTE trial[11] for the treatment of adult venous thrombosis and the inhibition of recurrence, compared to warfarin, edoxaban, a factor Xa inhibitor, showed noninferiority in terms of effectiveness and superiority in terms of safety, such as for bleeding.

In young patients with few thrombi, it originally was difficult to determine whether microvascular TE leads to Fontan circulatory insufficiency. In the past, it was said that following the Fontan procedure, elevated CVP, low output, and hepatopathy reduce various anticoagulation factors. However, Odegard et al.[12] reported that in children with HLHS, the risks of thrombosis include markedly elevated factor VIII levels and reduced protein C levels. In contrast, Tomkiewicz-Pajak et al.[13] reported that in adults undergoing the Fontan procedure, all coagulation factors, including factor VIII, were low but at the lower limit of normal. Although low levels of coagulation factors are characteristic, bleeding is not common, and elevated prothrombin fragment $F1+2$, which is a marker of thrombin generation, with an elevated tissue factor pathway inhibitor gives rise to the hypothesis that low coagulation factors might be a compensatory reaction to abundant thrombin generation. It has also been reported that increased activity of thrombin activatable fibrinolysis inhibitors impairs the fibrinolytic system and that vWF is high, which could be evidenced following the Fontan procedure; pulmonary blood flow that is not a pulse wave, slow-flowing systemic veins, and hypoxia lead to endothelial dysfunction. Moreover, following the Fontan procedure in adults with a history of embolism, platelet activation

has been found to increase P-selectin exposed on the membrane surface, as well as soluble CD40 ligand, and platelet activity has been found to be enhanced. This is the reason for supporting antiplatelet therapy. However, in activated endothelial cells in vascular impairment, low-dose aspirin therapy does not adequately inhibit proteins expressed by platelets, such as CD40 ligands,[14] and further examination is warranted. In other words, following the Fontan procedure, it is possible that adults could have various abnormalities, such as increased platelet activation, endothelial dysfunction, increased thrombin generation, and fibrinolytic system impairment. If the bleeding as a side-effect could be overcome, then the combined administration of anticoagulants and antiplatelets might be ideal. If increased thrombin generation is a problem, then new anticoagulants, such as antithrombin agents, could be promising, and a novel platelet aggregation inhibitor that is better than aspirin also needs to be developed.

In the present study, patients who had cerebral infarction as very long-term sequelae were only those initially considered to be at a high risk, with a residual pulmonary artery stump, concurrent pulmonary arteriovenous fistula, and a history of atrioventricular valve replacement. Unfortunately, the congealing fibrinogenolysis system was not examined in detail at the time of cerebral infarction onset and the cause of thrombus formation was not examined. A residual pulmonary artery stump has been reported to be extremely dangerous,[15] and the results of the present study suggested that the combined use of warfarin and aspirin could be insufficient in high-risk patients. Thus, either TEE should be performed proactively, warfarin used at a higher dose, or surgery be considered.

In the patient who died of pulmonary hemorrhage and refused to undergo contrast-enhanced angiography, back flow of the descending aorta was not confirmed on CT and echography to examine the collateral vessels. It is highly likely that the pulmonary hemorrhage was caused by abnormal collateral arteries, and we believe that cardiac catheterization should have been recommended actively. The other two patients were successfully treated by discontinuing aspirin and reducing the dose of warfarin. However, in the patient with diffuse alveolar hemorrhage, the bleeding repeated even after embolization of the abnormal vessels, and while the underlying mechanism was unclear upon initiation of low-dose macrolide

therapy, a reduction in the hemoptysis was observed. In recent years, macrolides have been reported to reduce pulmonary neutrophils, reduce IL-8, and inhibit neutrophilic inflammation of the airway,[16] and it is thought that they could improve pneumonopathy.

With regards to complications of gastrointestinal bleeding, in the present study, among patients administered aspirin at a low dose of 1–2 mg/kg/day combined with warfarin, some suffered ulceration that led to massive bleeding. In particular, patients with aspirin-related ulceration might not complain of abdominal pain. Among our patients, only one complained of abdominal pain. Even with mild ulceration without abdominal pain, it should be kept in mind that massive hemorrhage can result with warfarin combination therapy in particular. Enteric-coated aspirin tablets are not the ultimate treatment, and ulceration in the small intestines has been reported in recent examinations using capsule endoscopy. Among patients receiving anticoagulant and antiplatelet therapy, ulceration should be considered in those without abdominal pain, with blood in the stool, and with gastrointestinal bleeding that develops suddenly into shock. For the prevention of aspirin-related ulceration, the combined use of PPIs is a common practice, and it has been reported that PPIs with H2 blockers are effective for primary protection.[17, 18] However, this issue has not been discussed in detail for pediatric cases. According to the "Clinical Practice Guidelines for Peptic Ulcers" published by the Japan Society of Gastroenterology in October 2009, PPIs are the first choice of drug, and in the treatment of stomach ulcers, it is hard initially to use H2 blockers and mucosal protective agents. While treatment should be flexible for each case, in adults considered to have no problem, there is the issue of whether gastric acid inhibition is safe over the long-term, and the examination of patients with congenital heart disease and young patients is needed.

Furthermore, it has been reported that, as an expected event, it is significantly common for adults to experience chronic venous insufficiency of the legs following the Fontan procedure.[19] In the future, there is concern that in patients following the Fontan procedure, thrombotic factors will become apparent with age and increase the incidence of thrombosis. To date, physician cooperation has been needed for the above; therefore, information regarding surgical methods, hemodynamics, and expected complications should be shared.

At present, explanations are given to patients undergoing the Fontan procedure and their families indicating that TE could occur, and that in the event of the appearance of symptoms suggestive of cerebral infarction, such as paralysis, they are instructed to present to a doctor via ambulance immediately for thrombolytic therapy. They are also told that as TE preventive agents can cause hemorrhagic complications, they should check for the presence or absence of blackish feces daily. Patients receiving aspirin in combination with warfarin should proactively consider the combined use of antiulcer agents. They are also instructed as necessary that even in the absence of hemoptysis, regular cardiac catheterization and angiography are needed to examine the presence or absence of abnormal vessels. In everyday life, when diarrhea develops, they are told that because of the inhibition of vitamin K absorption, warfarin can be too effective and that antimicrobials inhibit the intestinal flora and affect metabolism, thereby increasing PT-INR. Moreover, even when PT-INR is within the therapeutic range, it is possible that small wounds may take time to stop bleeding. Therefore, it is recommended to purchase an alginate dressing that promotes hemostasis.

In the present study, gastrointestinal bleeding was common in children and youths, whereas cases at a high risk of infarction tended to be seen only in adulthood. This seems to support the discontinuation of warfarin for several years postoperatively, then recommencing the agent in adulthood. However, at present, no patients at our department have undergone follow-up observation with aspirin monotherapy. Therefore, we cannot compare the anticoagulant and antiplatelet groups. Furthermore, at our hospital, cardiac catheterization is not performed on a patient without undergoing the Fontan procedure. Therefore, pulmonary vascular resistance was not examined in detail. It does not appear to be a problem that can be solved quickly through performing further random sampling tests via an enrollment system of Fontan procedure patients and comparative studies of Fontan circulatory insufficiency, such as the detailed shift in pulmonary vascular resistance in multicenter prospective collaborative studies, and the presence or absence of thrombi by regular TEE. We hope the day will arrive when we are able to explain to patients with confidence whether warfarin should be discontinued for several years postoperatively and then recommended in adulthood, whether aspirin and

warfarin should be used for life together with PPIs and H2 blockers to prevent silent emboli and maintain good Fontan circulation, and whether a novel anticoagulant would be more effective.

Conclusions

In Fontan circulation, pulmonary circulation is not a pulse wave, and the presence of abnormalities in coagulation and the fibrinolytic system is said to promote platelet activity, for which the combined use of anticoagulant and antiplatelet therapy is reportedly effective. In the future, an evidence-based strategy is needed to determine whether the combined use of aspirin and warfarin ensures good Fontan circulation. When providing treatment, utmost attention should be paid to hemorrhagic complications and the choice of drug should be examined on an individual basis.

Furthermore, a system is required wherein rapid support can be obtained from physicians in various fields, including the Department of Cardiovascular Medicine, Department of Gastroenterology, and Department of Cerebrovascular Medicine.

Conflicts of Interest

The author has no conflicts of interest to declare.

References

1) Khairy P, Fernandes SM, Mayer JE Jr, et al: Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. Circulation 2008; **117**: 85–92

2) Watson T, Shantsila E, Lip GY: Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. Lancet 2009; **373**: 155–166

3) Varma C, Warr MR, Hendler AL, et al: Prevalence of "silent" pulmonary emboli in adults after the Fontan operation. J Am Coll Cardiol 2003; **41**: 2252–2258

4) Monagle P, Cochrane A, Roberts R, et al: Fontan Anticoagulation Study Group: A multicenter, randomized trial comparing heparin/warfarin and acetylsalicylic acid as primary thromboprophylaxis for 2 years after the Fontan procedure in children. J Am Coll Cardiol 2011; **58**: 645–651

5) McCrindle BW, Manlhiot C, Cochrane A, et al: Fontan Anticoagulation Study Group: Factors associated with thrombotic complications after the Fontan procedure: A secondary analysis of a multicenter, randomized trial of primary thromboprophylaxis for 2 years after the Fontan procedure. J Am Coll Cardiol 2013; **61**: 346–353

6) Connolly S, Pogue J, Hart R, et al, ACTIVE Writing Group of the ACTIVE Investigators: Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): A randomised controlled trial. Lancet 2006; **367**: 1903–1912

7) Manlhiot C, Brandao LR, Kwok J, et al: Thrombotic complications and thromboprophylaxis across all three stages of single ventricle heart palliation. J Pediatr 2012; **161**: 513–519

8) Uno Y, Morita K, Yamashiro M, et al: Postoperative changes of coagulability and fibrinolytic function in Fontan circulation: Possibility of the conversion of anticoagulation therapy. Pediatric Cardiology and Cardiac Surgery 2010; **26**: 49–53

9) Ohuchi H, Yasuda K, Miyazaki A, et al: Prevalence and predictors of haemostatic complications in 412 Fontan patients: Their relation to anticoagulation and haemodynamics. Eur J Cardiothorac Surg 2015; **47**: 511–519

10) Hallas J, Dall M, Andries A, et al: Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: Population based case-control study. BMJ 2006; **333**: 726

11) Büller HR, Décousus H, Grosso MA, et al, Hokusai-VTE Investigators: Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 2013; **369**: 1406–1415

12) Odegard KC, Zurakowski D, DiNardo JA, et al: Prospective longitudinal study of coagulation profiles in children with hypoplastic left heart syndrome from stage I through Fontan completion. J Thorac Cardiovasc Surg 2009; **137**: 934–941

13) Tomkiewicz-Pajak L, Hoffman P, Trojnarska O, et al: Abnormalities in blood coagulation, fibrinolysis, and platelet activation in adult patients after the Fontan procedure. J Thorac Cardiovasc Surg 2013; **13**: 650–658

14) Giannini S, Falcinelli E, Bury L, et al: Interaction with damaged vessel wall in vivo in humans induces platelets to express CD40L resulting in endothelial activation with no effect of aspirin intake. Am J Physiol Heart Circ Physiol 2011; **6**: 2072–2079

15) Lee SY, Baek JS, Kim GB, et al: Clinical significance of thrombosis in an intracardiac blind pouch after a Fontan operation. Pediatr Cardiol 2012; **1**: 42–48

16) Walkey AJ, Wiener RS: Macrolide antibiotics and survival in patients with acute lung injury. Chest 2012; **141**: 1153–1159

17) Yeomans N, Lanas A, Labenz J, et al: Efficacy of esomeprazole (20 mg once daily) for reducing the risk of gastroduodenal ulcers associated with continuous use of low-dose aspirin. Am J Gastroenterol 2008; **103**: 2465–2473

18) Taha AS, McCloskey C, Prasad R, et al: Famotidine for the prevention of peptic ulcers and oesophagitis in patients taking low-dose aspirin (FAMOUS): A phase III, randomized, double-blind, placebo-controlled trial. Lancet 2009; **374**: 119–125

19) Valente AM, Bhatt AB, Cook S, et al, AARCC (Alliance for Adult Research in Congenital Cardiology) Investigators: The CALF (Congenital Heart Disease in Adults Lower Extremity Systemic Venous Health in Fontan Patients) study. J Am Coll Cardiol 2010; **56**: 144–150