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A Multifaceted Approach to the Management of Plastic Bronchitis after Cavopulmonary Palliation

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Abstract

Background—Plastic bronchitis is a rare, potentially life-threatening complication after Fontan operation. Hemodynamic alterations (elevated central venous pressure and low cardiac output) likely contribute to the formation of tracheobronchial casts composed of inflammatory debris, mucin, and fibrin. Pathologic studies of cast composition support medical treatment with fibrinolytics such as inhaled tissue plasminogen activator (t-PA).

Methods—Retrospective case series of medical, surgical, and catheter-based management of patients with plastic bronchitis after cavopulmonary palliation.

Results—Fourteen patients (86% male, 93% white) were included. Median age at Fontan operation was 2.7 years (range 1.2–4.1) with median interval to plastic bronchitis presentation of 1.5 years (9 days–15.4 years). Cast composition was available for 11 patients (79%) and included fibrin deposits in 7. All patients were treated with pulmonary vasodilators. Thirteen patients (93%) were treated with inhaled t-PA. Hemodynamically significant lesions in the Fontan pathway were addressed via catheter-based (n=9) and surgical (n=3) interventions. Three patients (21%) underwent heart transplantation. Median length of follow-up was 2.7 years (0.6–8.7). Symptoms improved such that six of thirteen (46%) patients were weaned off t-PA. Rare or episodic casts are successfully managed with outpatient t-PA in the majority of other patients. Of the 3 patients who underwent heart transplant, two are asymptomatic and one has recurrent casts in the setting of elevated filling pressures and rejection.

Conclusions—A systematic step-wise algorithm, which includes optimization of hemodynamics, aggressive pulmonary vasodilation and inhaled t-PA, is an effective treatment strategy for patients with plastic bronchitis after cavopulmonary connection.

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Keywords

Congenital heart disease; Fontan; lung

Introduction

Plastic bronchitis is a rare, potentially life-threatening complication of the Fontan operation, the final palliative procedure for various forms of single ventricle heart disease [1–6]. Plastic bronchitis is characterized by the formation of rubbery casts of the tracheobronchial tree that may cause cough, wheezing, dyspnea, and hypoxia; progressive airway obstruction may lead to asphyxia and death. Although plastic bronchitis has been described in patients with respiratory disorders including severe asthma, allergies, cystic fibrosis, and sickle cell acute chest syndrome [7–9], it appears to occur most commonly in patients with congenital heart disease and Fontan circulation. The true prevalence of plastic bronchitis after Fontan is unknown as diagnosis depends on direct visualization of a cast after expectoration or on bronchoscopy. Some estimate the prevalence of the disorder to be as high as 4–14% in patients with Fontan circulation [10].

The pathogenesis of plastic bronchitis after Fontan is largely unknown. Hemodynamic alterations inherent in the Fontan circulation (elevated central venous and pulmonary artery pressures, relatively low cardiac output) likely contribute in some manner to a break in mucosal integrity and injury to the alveolar-capillary barrier [11]. Leakage of proteinaceous and cellular material into the airways results in cast formation. However, there is often a disconnect between an individual patient's Fontan hemodynamics (i.e. degree of central venous hypertension) and the development of plastic bronchitis. It is unclear why a minority of patients develop plastic bronchitis and others do not.

Given the unclear pathogenesis of plastic bronchitis, treatment regimens are based on case reports and anecdotal data. Anti-inflammatory agents, bronchodilators, antibiotics, and mucolytics along with aggressive pulmonary toilet may decrease disease severity [12]. Treatment with pulmonary vasodilators may increase cardiac output by decreasing pulmonary vascular resistance and augmenting ventricular filling [13]. Plastic bronchitis may resolve after surgical or catheter-based interventions to improve hemodynamics or after cardiac transplantation [12]. Additionally, aerosolized tissue plasminogen activator (t-PA) is an important treatment option that may decrease cast burden and improve clinical symptoms in patients with plastic bronchitis after Fontan [1,2,20,21].

Despite absence of a complete understanding of the pathophysiology of plastic bronchitis after Fontan, a standardized protocol and management strategy may offer a pathway for successful outcome for this life-threatening condition. Each patient with single ventricle is unique as to how they develop plastic bronchitis, however thematic commonalities may be evident. The objective of this report is to describe the experience with medical, catheter-based, and surgical treatment of plastic bronchitis at our institution over the last 10 years, providing insight into the evolution of our current management scheme for this disease.

Patients and Methods

All patients with a clinical or pathologic diagnosis of plastic bronchitis managed through the Single Ventricle Survivorship Program at the Children's Hospital of Philadelphia (CHOP) between 1/1/2003 and 8/22/2013 were eligible for inclusion in this retrospective case series. Hospital charts were reviewed for demographic information and pertinent clinical characteristics. Demographic and anatomic characteristics were summarized by standard descriptive summaries and expressed as means $\pm$ standard deviations and percentages.

The study protocol was approved by CHOP's Institutional Review Board (IRB # 13-010445).

Results

Fourteen patients met inclusion criteria. Demographic characteristics are summarized in Table 1. Patients were 86% male, 93% white. Six patients (43%) had hypoplastic left heart syndrome. Thirteen patients underwent Fontan completion at median age of 2.7 years (range 1.2–4.1) with an extra-cardiac conduit in 6 (46%), lateral tunnel in 6 (46%), and catheter-based covered stent baffle (performed at an outside institution) in 1 patient (8%). One patient was not deemed a Fontan candidate given a limited pulmonary vascular bed and history of venous thrombosis; the patient remains with superior cavopulmonary connection. Twelve (92%) Fontan subjects were fenestrated at the time of initial operation.

Four patients had persistent pleural effusions for more than 2 weeks after Fontan operation. One of these patients required brief extra-corporal membrane oxygenation (ECMO) support in the immediate post-operative period, then had persistent pleural drainage for more than three weeks post-operatively. The patient expectorated casts on post-operative day 22 and was subsequently converted back to a Glenn circulation given the early development of plastic bronchitis in the setting of persistent pleural drainage and elevated Fontan pressures. Conversion to a Glenn circulation was achieved through catheter techniques. Two patients developed late-onset pleural effusions several months (3 and 5 months) after Fontan operation. The patient who developed effusions at 5 months was found to have thrombotic Fontan occlusion requiring revision.

Median time from Fontan to plastic bronchitis presentation was 1.5 years (9 days–15.4 years). Two patients developed symptoms within 1 month of Fontan (post-operative days 9 and 22). All patients had a history of cast expectoration at diagnosis (Figure 1). Two patients had life-threatening airway obstruction and cardiorespiratory failure; one required ECMO while the other required emergent intubation and suffered multisystem organ dysfunction. Five patients had a history of prolonged cough, repeated respiratory infections, or chronic dyspnea several months to years prior to cast expectoration.

Echocardiograms from plastic bronchitis presentation were available in 12 patients (86%). Most patients had normal or low normal ventricular function with little or no atrioventricular valve regurgitation (Table 1).

Thirteen patients underwent cardiac catheterization at most 6 months from plastic bronchitis presentation. Median pressures were 15.5 mm Hg (range 10–28) in the Fontan baffle and 8 (4–16) in the ventricle at end-diastole. Pulmonary vascular resistance was 1.6 (1.1–4.4) indexed Wood units, and cardiac index was 3.3 (2.5–4) L/min/m². Hemodynamic data for individual subjects is presented in Table 1.

Pathologic reports from bronchoscopy specimens or expectorated casts were available for 11 patients (79%). Cast composition included fibrin deposits in 7 patients, while the casts of 4 patients showed evidence of inflammatory infiltrate only.

Table 2 details treatment strategies for the included patients. Medical management included some combination of bronchodilators, mucolytics, and inhaled steroids in all patients. Many patients received vest physiotherapy to provide aggressive pulmonary toilet. One patient was receiving chronic oral steroid treatment upon presentation to our institution. All patients were treated with the pulmonary vasodilator sildenafil, the most common dose being 20 mg three times daily. Bosentan was used as an additional pulmonary vasodilator in three patients. Carvedilol was used in five patients to slow heart rate and to potentially encourage ventricular filling. Digoxin was used when plastic bronchitis symptoms recurred in the setting of congestive heart failure.

Thirteen patients were treated with inhaled t-PA; the t-PA dose was 4 mg (4 mL) inhaled 2–4 times per day. One patient experienced significant epistaxis due to elevated INR while on t-PA, warfarin, and aspirin. A few months later, this same patient experienced epistaxis, purpura, and coagulopathy due to an accidental warfarin overdose. Anticoagulants and t-PA were held until the error was discovered. The patient recovered without incident.

Nine patients underwent catheter-based interventions to relieve hemodynamically significant residual or recurrent lesions at the time of plastic bronchitis diagnosis (Table 2). A catheter-based strategy was employed to convert one previously mentioned patient from a Fontan to a Glenn circulation. A vascular device was placed in the superior aspect of the Fontan baffle to occlude inferior vena cava flow to the pulmonary arteries, and a large stent was deployed across the fenestration proximally.

Surgical interventions to address hemodynamically significant lesions at or soon after plastic bronchitis presentation were performed in 3 patients (Table 2). One patient developed symptoms 8.3 months after Fontan. Atrial septal restriction was demonstrated on echocardiogram and cardiac catheterization, so atrial septectomy with unroofing of the coronary sinus was performed. Another patient developed plastic bronchitis 7 months after Fontan. This patient had previously undergone Fontan revision due to thrombotic occlusion in the setting of late-onset pleural effusions (described above). Cardiac catheterization at plastic bronchitis presentation demonstrated stenosis at the inferior vena cava (IVC)-Fontan junction so both the IVC and fenestration were stented. After several cast-free months, casts returned in the setting of a viral respiratory infection. Angiography demonstrated an unobstructed Fontan pathway but limited fenestration flow. Dilation of the fenestration stent was complicated by thrombotic occlusion of the fenestration resulting in low cardiac output prompting a second Fontan revision.

Three patients underwent cardiac transplantation at 0.9, 1.5, and 2.5 years from development of plastic bronchitis symptoms. The patient who was transplanted 0.9 years from plastic bronchitis presentation had marked cyanosis and exercise intolerance after fenestration dilation and persistent casts despite t-PA therapy. The patient who was transplanted 1.5 years from plastic bronchitis presentation had elevated filling pressures in the setting of left ventricular outflow tract obstruction and moderate to severe mitral valve regurgitation. The patient underwent sub-aortic stenosis resection and prosthetic mitral valve replacement. However, ventricular function declined and severe plastic bronchitis symptoms persisted so the patient underwent heart transplant. The patient who was transplanted 2.5 years from plastic bronchitis presentation initially improved symptomatically after fenestration creation and stenting. However, severe plastic bronchitis symptoms recurred nearly 1 year after the intervention. Casts persisted despite t-PA therapy, and the patient required 2 hospital admissions for airway obstruction prior to transplant.

Median length of follow-up since presentation to our institution was 2.7 (0.6–8.7) years. Current status is detailed in Table 2. Post-transplant patients were weaned off t-PA; 2 of 3 patients remain asymptomatic since transplant. Of the 10 patients with palliated circulation with a history of t-PA treatment, 3 have been weaned off t-PA while 7 continue on treatment. The majority of patients have no, or rare episodic cast formation that is successfully managed with outpatient re-initiation of t-PA. Cast recurrence is commonly associated with upper respiratory infection.

Comment

Our experience demonstrates that plastic bronchitis after Fontan operation can be successfully managed with either complete elimination or substantial reduction in symptoms. This is achieved through a step-wise, individually tailored strategy aimed at improving Fontan circulation through pharmacologic, catheter-based and/or surgical treatments, in combination with aggressive use of aerosolized t-PA to maintain airway patency (Table 3).

Plastic bronchitis is a serious, potentially life-threatening complication of the palliated single ventricle circulation. Goals of management include 1) optimization of Fontan hemodynamics as the foundation of the condition and 2) alleviation of symptoms. Treatment with pulmonary vasodilators including sildenafil and bosentan may decrease pulmonary vascular resistance and augment ventricular filling, thereby increasing cardiac output [14]. Additionally, carvedilol may decrease end-diastolic pressure and improve ventricular filling through its mechanism of heart rate reduction. Aggressive use of these agents may improve the circulatory limitations inherent in every Fontan patient, thereby altering the threshold for bronchial cast formation.

Catheter- or surgical-based interventions to relieve recurrent or residual hemodynamic lesions should be pursued in the management of plastic bronchitis. Lesions or defects that increase Fontan pressures at any point along the “circuit” may theoretically cause leakage of cast components into the airway via a break in mucosal integrity and injury to the alveolar-capillary barrier. In our experience, interventions to address ventricular outflow tract

obstruction, atrioventricular valve regurgitation, pulmonary venous obstruction, pulmonary artery stenosis, and Fontan baffle obstruction resulted in decreased cast formation. Additionally, fenestration of the systemic venous pathway may decrease Fontan pressures and improve cardiac output through right to left shunting [14]. When the Fontan circulation “fails” or symptoms are unmanageable, plastic bronchitis may resolve after cardiac transplantation [15,16]. The multi-center Pediatric Heart Transplant Study reported outcomes in 10 single ventricle patients with plastic bronchitis who underwent heart transplantation between 1993 and 2009 [17]. Seven of ten patients survived at least 30 days post-transplant; none of the surviving patients had recurrence of casts at a mean of 5.7 years post-transplant. In our series, 2 of 3 patients remain asymptomatic post-transplant. One patient was symptom-free for several years, but recently experienced recurrent casts in the setting of rejection and elevated central venous pressure – lending support to the role of elevated central venous pressure in plastic bronchitis pathogenesis.

Anti-inflammatory agents, bronchodilators, antibiotics, and mucolytics may decrease symptom severity and are important components of the treatment regimen. However, recent pathologic studies of cast composition suggest a more mechanistic approach to treatment. Traditional classification of plastic bronchitis differentiates between cellular and acellular casts – cellular casts are composed of inflammatory debris and infiltrate while acellular casts are composed of mucin and fibrin [18]. Patients with cellular casts may improve symptomatically when treated with inhaled corticosteroids. Acellular casts have been considered unique to plastic bronchitis associated with congenital heart disease and the optimal therapy is not as clear. However, overlap of pathologic classification has now been seen in plastic bronchitis following the Fontan operation [8]. Analysis of cast composition suggests that casts are composed primarily of fibrin despite being highly cellular with a lymphocytic predominance [19]. Our series supports this finding, with fibrin deposits present in 7 of 11 patients with available cast pathology. Reflective of this pathologic overlap, corticosteroids have been reported to decrease cast burden even in acellular casts associated with Fontan physiology [12]. While the mechanism is unclear, mild airway inflammation may be superimposed on mucosa injured by altered Fontan hemodynamics.

Additionally, clinical use of fibrinolytics such as inhaled t-PA is supported by existing data and by ex-vivo analysis of cast responsiveness to t-PA [19]. Our experience is in agreement with several small case-reports suggesting that t-PA is a safe and effective treatment of plastic bronchitis after Fontan [1,2,20,21]. Our preferred dose of 4 mg inhaled 2–4 times daily has been effective in reducing cast burden and allowing outpatient management of symptoms in several patients in our series. The only minor complication we have experienced is epistaxis, which may be exacerbated by treatment with anti-coagulants and anti-platelet agents.

Finally, lymphatic malformations and endobronchial lymph leakage may contribute to cast formation [22]. Reports of chyle in plastic bronchitis casts suggest that pulmonary lymph flow may be abnormal and may be a potential treatment target [23]. Innovative surgical approaches, including diversion of the innominate vein to the atria, attempt to decompress the thoracic duct and improve lymph flow in the failing Fontan circulation [24]. We presented one patient with resolution of symptoms after catheter-based oil and glue

embolization of lymphatic collaterals originating from the thoracic duct [25]. Increased understanding of the Fontan lymphatic system and its alterations under elevated central venous pressure is necessary and may be possible with novel MRI imaging techniques [26]. A strategy that combines relief of anatomic obstruction in the Fontan pathway and vigorous pulmonary vasodilation with catheter-based occlusion of well-mapped, isolated sites of lymphatic leakage into the airways may ultimately be the ideal management plan. Further investigation and longer follow-up is necessary to assess the efficacy of these lymphatic interventions.

In conclusion, this case series describes our experience in management of patients with plastic bronchitis after Fontan completion. While the relative efficacy must be considered within an individual clinical scenario, this series supports the use of a systematic step-wise algorithm, which includes pulmonary vasodilators as well as inhaled t-PA, as an effective treatment strategy for most patients with this condition (Table 3). Larger multicenter studies are needed to better understand the pathogenesis of plastic bronchitis in order to potentially prevent its development.

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Figure 1.
Expectorated cast from a patient with plastic bronchitis after Fontan operation.

Patient demographics and characteristics

Table 1

Gender	Diagnosis	Fontan type	Fen ^a	Interval between Fontan and PB symptoms	Hemodynamic characteristics at PB presentation					
					Vent fcn ^b	AVVR ^b	Fontan pressure (mm Hg)	Vent EDP (mm Hg)	Cardiac Index (L/min/m ²)	PVRI (WU)
1 M	TA, TGA, PS	LT	Y	15.4 y	Normal	Mild-moderate	21	16	2.6	1.9
2 M	CCAVC(L), TGA, sub AS	LT	Y	13.1 y	Normal	Trivial	13	7	3.3	1.6
3 M	HLHS	LT	Y	9.3 y	n/a ^c	n/a	11	7	n/a	n/a
4 F	CCAVC(L), PS	CS	N	2.6 y	Normal	Mild	13	9	2.5	1.3
5 M	HLHS	ECC	Y	3.1 y	n/a	n/a	n/a	n/a	n/a	n/a
6 M	CCAVC(R), RV-Aorta, PA, TAPVR ^d	ECC	Y	1.2 y	Normal	Trivial	18	10	4	1.5
7 M	HLHS	LT	Y	8.3 m	Normal	Trivial	20	8	3.2	1.3
8 M	CCAVC(R), AA	LT	Y	2.6 y	Mildly depressed	Moderate-severe	10	4	3	2.3
9 M	PA/IVS	ECC	Y	9 d	Normal	None	11	5	3.4	1.1
10 M	DORV, VSD, PS	ECC	Y	7.0 m	Low normal	None	28	10	n/a	n/a
11 M	HLHS	ECC	Y	1.5 y	n/a	n/a	15	10	3.9	2.1
12 M	HLHS	ECC	Y	22 d	Normal	None	21	15	n/a	n/a
13 M	CCAVC(R), DORV, PA, TAPVR ^d	LT	Y	6.9 m	n/a	n/a	16	5	n/a	1.5
14 F	HLHS ^e	n/a	n/a	n/a	Moderately depressed	Mild-moderate	Other ^f	5	n/a	4.4

^a at time of Fontan completion;^b by echocardiogram;^c n/a = data not available;^d Heterotaxy syndrome;^e Remains with Hemi-Fontan physiology, not a Fontan candidate;

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f Pulmonary artery pressure = 9 mm Hg;

Fen, Fontan fenestration; PB, plastic bronchitis; Vent fxn, ventricular function; AVVR, atrioventricular valve regurgitation; EDP, end-diastolic pressure; PVRI, pulmonary vascular resistance indexed to body surface area; WU, Wood units; TA, tricuspid atresia; TGA; transposition of the great arteries; PS, pulmonary stenosis; LT, lateral tunnel; y, years; CCAVC(L), complete common atrioventricular canal unbalanced to the left; AS, aortic stenosis; HLHS, hypoplastic left heart syndrome; n/a, data not available; CS, covered stent; ECC, extracardiac conduit; CCAVC(R), complete common atrioventricular canal unbalanced to the right; RV-Aorta, right ventricular origin of the aorta; PA, pulmonary atresia; TAPVR, total anomalous pulmonary venous return; m, months; AA, aortic atresia; IVS, intact ventricular septum; DORV, double outlet right ventricle; VSD, ventricular septal defect; d, days

Table 2

Treatment strategies and current symptoms

	Medical management ^a	Catheter-based interventions	Surgical interventions	Heart transplant	Current status
1	Azithromycin, sildenafil, inhaled t-PA		Prosthetic mitral valve replacement and resection of sub AS	Y	Resolution of symptoms off t-PA for > 3 years post-OHT; recent recurrence of casts in the setting of presumed rejection and elevated CVP
2	Azithromycin, sildenafil, inhaled t-PA	Balloon dilation of fenestration		Y	Asymptomatic; off t-PA for 3 years since OHT
3	Sildenafil, inhaled t-PA, carvedilol	Creation and stenting of fenestration		Y	Asymptomatic; off t-PA for > 2 years since OHT
4	Azithromycin, lasix, digoxin, carvedilol	Creation and balloon dilation of fenestration, LPA stenting		N	Asymptomatic for 1.5 years; never required t-PA
5	Sildenafil, inhaled t-PA	Balloon dilation of LSVc and RPA stents		N	Recurrence of casts, ventricular dysfunction and PLE; continues on outpatient t-PA
6	Sildenafil, inhaled t-PA	Balloon dilation and stenting of fenestration, RPV dilation		N	Only small casts since fenestration stented; continues on outpatient t-PA
7	Sildenafil, inhaled t-PA		Resection of atrial septum and unroofing of coronary sinus	N	Asymptomatic for > 2.5 years since surgical procedure; t-PA weaned off
8	Sildenafil, inhaled t-PA			N	Rare, episodic casts in the setting of viral infections; t-PA weaned off
9	Sildenafil, inhaled t-PA, bosentan	Balloon dilation and stenting of fenestration, dilation of LPV stent, embolization of APCs		N	Extremely rare casts; marked decrease in cast burden after addition of bosentan; continues on outpatient t-PA
10	Sildenafil, inhaled t-PA, carvedilol	Stenting of IVC and fenestration	Fontan revision and patch augmentation of RPVs	N	Asymptomatic for 3 months since Fontan revision; continues on outpatient t-PA
11	Sildenafil, inhaled t-PA	Coil embolization of V-V collateral; glue embolization of TD lymphatic collaterals		N	No casts with resolution of chronic cough after lymphatic intervention; t-PA weaned off
12	Sildenafil, inhaled t-PA, bosentan, carvedilol	Catheter-based strategy to take down to Glenn physiology		N	Very small rare casts; marked decrease in cast burden after addition of bosentan; continues on outpatient t-PA
13	Chronic oral steroids, sildenafil, inhaled t-PA, bosentan, carvedilol, digoxin			N	Rare casts; marked decrease in cast burden since addition of bosentan and carvedilol; continues on outpatient t-PA
14	Sildenafil, inhaled t-PA			N	Fewer casts since recently starting outpatient t-PA

^a All patients were treated with some combination of bronchodilators, mucolytics, and inhaled steroids

t-PA, tissue plasminogen activator; AS, aortic stenosis; OHT, orthotopic heart transplant; CVP, central venous pressure; LPA, left pulmonary artery; LSVc, left superior vena cava; RPA, right pulmonary artery; PLE, protein-losing enteropathy; RPV, right pulmonary vein; LPV, left pulmonary vein; APCs, aortopulmonary collateral vessels; IVC, inferior vena cava; V-V, vena-venous; TD, thoracic duct

Table 3

Treatment algorithm for plastic bronchitis after Fontan operation. Following diagnostic evaluation patients commence with phase 1 therapy. After a period of time if no adequate response, then treatment may move on to phase 2 which is added on to phase 1. If still no response, then phase 3 is considered.

Diagnostic Evaluation	<ul style="list-style-type: none"> • Echo • Cardiac MRI • Cardiac catheterization and hemodynamic assessment • Bronchoscopy (diagnostic, as well as potentially therapeutic for occluded airways)
Phase 1 Therapy	<ul style="list-style-type: none"> • Treat abnormal findings on diagnostic evaluation (relieve anatomical obstruction to systemic or pulmonary venous return) • Bronchodilators, mucolytics, inhaled steroids, aggressive pulmonary toilet • Aggressive pulmonary vasodilation, first with PDE-5 inhibition (eg. Sildenafil, Tadalafil) then add endothelin-1 inhibition (Bosentan) • Treat airway obstruction and maintain airway patency with use of daily aerosolized t-PA
Phase 2 Therapy	<ul style="list-style-type: none"> • Carvedilol use to improve ventricular filling • Fenestration creation
Phase 3 Therapy	<ul style="list-style-type: none"> • Fontan take-down to Glenn or shunt physiology • Heart transplantation
New Therapy	<ul style="list-style-type: none"> • Lymphatic system imaging and catheter-based embolization of peribronchial lymphatic channels