Chapter 3
The Link Between Lymphatic Obstruction and Congenital Heart Disease

Manish Bansal

Abstract There is a complex interplay between congenital heart disease and lymphatic obstruction as evidenced by the literature where associations have been reported between lymphatic impairment and congenital heart disease. Turner syndrome is a classic example of a condition where lymphatic impairment might be the cause of some congenital heart diseases. At the same time there are congenital heart diseases which impair the lymphatic flow, leading to significant morbidity and mortality; these include left-to-right shunt lesions and protein-losing enteropathy. Congenital cardiac surgery which involves extensive mediastinal dissection can also cause injury to the lymphatic system. Hence, the lymphatic system must be given importance while managing patients with congenital heart disease.

Keywords Congenital heart disease • Lymphatic obstruction • Turner syndrome • Cardiac surgery • Protein-losing enteropathy

Introduction

The lymphatic system maintains homeostasis by receiving proteins and excess fluid from the interstitial spaces and returning them to the venous system [1]. Large lymphatic channels travel with the major coronary arteries in the epicardium and small lymphatics can be found in the endocardium [2]. Impairment of cardiac lymphatic flow has been known to be associated with ventricular fibrillation, increased

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superior vena cava pressures, and pulmonary arterial hypertension [3]. Many congenital heart surgeries involve excision or destruction of the intrathoracic and mediastinal lymphatics, primarily because it is assumed that the mediastinal lymphatic system is surgically expendable. However, obstruction of the cardiac lymphatic obstruction may lead to cardiac dysfunction and cardiac lymph edema [4]. Similarly, pulmonary lymphatic obstruction can cause pulmonary perivascular lymphedema, endothelial injury, and pulmonary arterial obstruction. In this chapter we will address the issue of cardiac lymphatic obstruction and its impact on congenital heart disease and vice versa.

Link Between Lymphatic Obstruction and Congenital Heart Disease

Increased Nuchal Translucency and Congenital Heart Disease

Increased nuchal translucency (NT) has been strongly associated with congenital heart disease [5]. This finding, as often happens, was a by-product of other studies that were primarily concerned with screening for chromosomal abnormalities. While risks for chromosomal abnormalities are adjusted for maternal age and serum biochemistry, risks for congenital heart disease appear to be solely dependent on the degree of NT itself.

Initially increased NT was thought to be associated with chromosomal abnormalities. Later it was found out that in euploid fetuses with increased NT, there is increased incidence of congenital heart diseases, the most common being the narrowing of the aortic isthmus [6]. The incidence of congenital heart disease in fetuses with increased NT and normal karyotype varies with the degree of NT, and approximately one third of fetuses with major congenital heart disease can potentially be identified by NT screening. Increased NT however does not predict the type of cardiac abnormality that may be encountered [5].

The etiology of increased NT has been widely debated with etiologies including cardiac heart disease itself, cardiac failure, and lymphatic system abnormalities. A mesenchyme-lined fluid-filled cavity (edema) was found in the posterior nuchal region together with a bilaterally enlarged jugular lymphatic system (JLS) in mutant mouse models (trisomy 16, equivalent to human trisomy 21) (Fig. 3.1) [7]. The persistent JLS were also seen by ultrasound in a large proportion of human fetuses with increased nuchal thickness. A possible delay in the development of the lymphatic vessels in the neck has been suggested to cause increased NT [8, 9]. The JLS is also the first part of the lymphatic system to develop, and a delay in such development of these vessels would lead to fluid accumulation in the neck region. As the process is only delayed, the fluid is eventually drained away when the JLS is finally able to reconnect to the venous system.

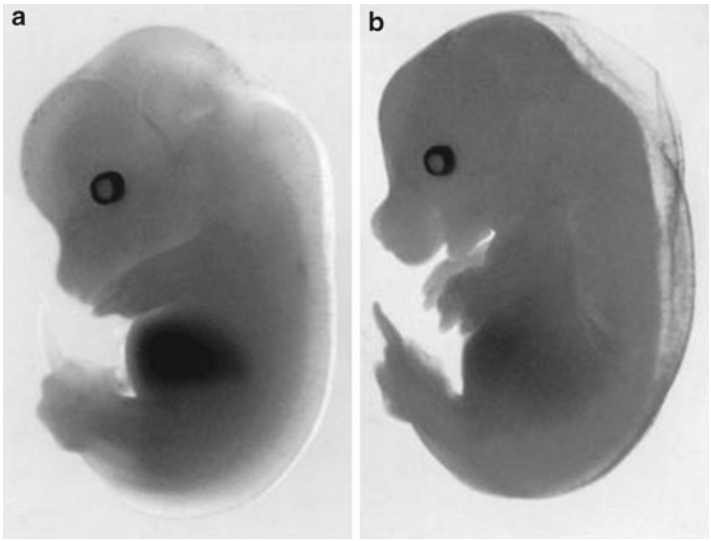

Fig. 3.1 Embryonic mouse. (**a**) Wild-type mouse embryo, day 14 of development. (**b**) Trisomy 16 embryo, day 14 of development with increased NT (Reprinted from Haak et al. [7] and used with permission of Elsevier)

Lymphatic Obstruction and Chromosomal Abnormalities

Disruption of the normal lymphatic system has been seen in patients with congenital heart diseases associated with various syndromes such as Turner and Noonan [10–12]. There is increased incidence of congenital heart disease in individuals with Turner syndrome, as well as neck webbing [13], which is formed from the postnatal residua of nuchal cystic hygromas caused by obstructed jugular lymphatics in utero. On the basis of this observation, Clark [13] proposed that centrally localized distended lymphatics compress the developing aortic root, resulting in specific left-sided defects, including hypoplastic left heart, bicuspid aortic valve, and coarctation of the aorta as a result of low flow. There are also specific right-sided defects that can occur, such as persistent left superior vena cava, anomalous pulmonary venous return, and dilated right atrium as a result of back pressure in response to obstructions in forward flow. This view was supported by further epidemiologic observations in a study of 120 infants with neck webbing reported in the Iowa Birth Defects registry, among which 66% were found to have flow-related defects [14]. These observations came from pathology studies which were focused on the most severely affected fetuses, raising the possibility that the association between congenital heart diseases and neck webbing simply reflects the most severe phenotype in 45, X individuals rather than a specific connection between these two phenotypic features of X-chromosome deletion [15].

However, in an observational study of Turner syndrome patients who were not selected for cardiovascular disease, a significant association was made between

central fetal lymphedema, signaled by neck webbing, and defects such as bicuspid aortic valve and coarctation of the aorta [15]. The anatomic defects associated with fetal lymphedema in Turner syndrome are decreased numbers of lymphatics and dilated lymphatic channels that end in distended sacs, which lack connections with the venous system. Severe lymphatic obstruction early in fetal development may cause heart failure from compression and/or impaired filling of developing cardiovascular structures, leading to fetal hydrops and demise [16]. Similarly, de Mooij et al. [17] demonstrated that Noonan syndrome fetuses of gestational age 16+0 weeks demonstrated nuchal edema and distended JLS with less tissue compared to the control fetuses.

Congenital Heart Disease and Its Effect on Lymphatic System

Congenital and acquired malformations of lymphatic circulation are well known in patients with congenital heart disease [15, 18–20]. Lymphangiectasis has been observed in infants and children with obstructive left-sided lesions, such as hypoplastic left heart syndrome with restrictive atrial septum [21, 22] or total anomalous pulmonary venous return [23]. Patients with lymphatic hypoplasia usually present with lymphoedema. Congenital heart disease is rare in these patients (a 1–4% incidence was described in one series [18]) and no particular cardiac lesion predominates. Similarly, lymphatic hyperplasia was not associated with any particular congenital heart disease, despite the incidence of 9.7% being greater than expected in the general population (0.9%) [19].

Congenital Heart Diseases Associated with Increased Pulmonary Blood Flow

Congenital heart diseases with increased pulmonary blood flow mainly include ventricular septal defects, atrial septal defects, atrioventricular canal defects, and patent ductus arteriosus. These are the most common types of congenital heart diseases. These patients often have significant morbidity which can be attributed to increased lung water, impairment of normal respiratory function, and increased metabolic burden on an already compromised cardiovascular system.

Increased pulmonary blood flow leads to increased capillary filtration of protein-poor fluid into the interstitial space and increased clearance of lymphatic fluid [24]. Reddy et al. [25] created an ovine model of chronically increased pulmonary blood flow by placing a large vascular graft between the aorta and pulmonary artery of a fetal lamb. Following spontaneous delivery, these lambs had increased pulmonary blood flow and demonstrated hemodynamic and morphologic features that mimicked the human disease. Acute increase in pulmonary blood flow can result in alterations in pulmonary vascular endothelial function including disruption in endothelium-dependent nitric oxide (NO) signaling [26].

Chronic increase in pulmonary blood flow leads to lymphatic alterations, including endothelial dysfunction, resulting in decreased lymphatic flow. There is decrease in protein-poor lymph flow which is less than expected for the increased pulmonary blood flow in such lesions [26]. These changes were seen in the ovine model, and they mimic the symptomatology of tachypnea and the failure to thrive seen in children with left-to-right shunt lesions. There is an increase in pulmonary capillary hydrostatic pressure in acute and chronic shunt due to an increase in pulmonary blood flow [26]. There is a decrease in lymphatic nitric oxide production, which could play a role in the perturbation of lymphatic function as well as the postnatal development of lymphatic network [27].

Lymphatic Obstruction and Protein-Losing Enteropathy

Protein-losing enteropathy (PLE) is a relatively uncommon complication of surgical procedures used for palliation of complex congenital heart disease. The relevant lymphatic circulation converges variably, but predictably, upon a discrete location in the central venous system (Fig. 3.2) [28, 29]. Hence, obstruction of the lymphatic system could be considered as one of the etiologies of PLE.

There have been studies demonstrating a link between lymphatic obstruction and congenital heart disease, especially in cases of PLE in patients undergoing Fontan operation [30]. In their retrospective case control study, Meadows et al. [30] found a relatively high prevalence (25%) of lymphatic disruption or central venous obstruction at the site of usual lymphatic drainage in patients with PLE when compared to controls (3%). Lymphatic obstruction was evident by MRI, angiography, or documented surgical thoracic duct ligation. Central venous catheter was not shown to be associated with PLE. This suggested that physical lymphatic obstruction may play an important, and previously unrecognized, role in the development of PLE in patients with complex congenital heart disease.

The lymphatic system in patients with Fontan physiology operates at, or near, its physiologic limit [31]. Elevated central venous pressure coherent to passive circulation in Fontan patients is transmitted to the hepatic and intestinal venous circulation, leading to increased lymph production [32]. At the same time, increased central venous pressure decreased the lymphatic return to central circulation [33, 34]. As a result, the lymphatic system operated at or near its physiological limit. There is subclinical enteric protein loss with rare decompensation to clinical PLE during unpredictable physiologic insults [35].

Lymphatic Obstruction and Left Heart Lesions

Hypoplastic left heart syndrome is one of the most extensively studied lesions, in relation to its effects on the lymphatic system. Data concerning other obstructive lesions is relatively sparse. Luciani et al. [36], in a report of a single patient with congenital pulmonary lymphagiectasis and hypoplastic left heart syndrome with a

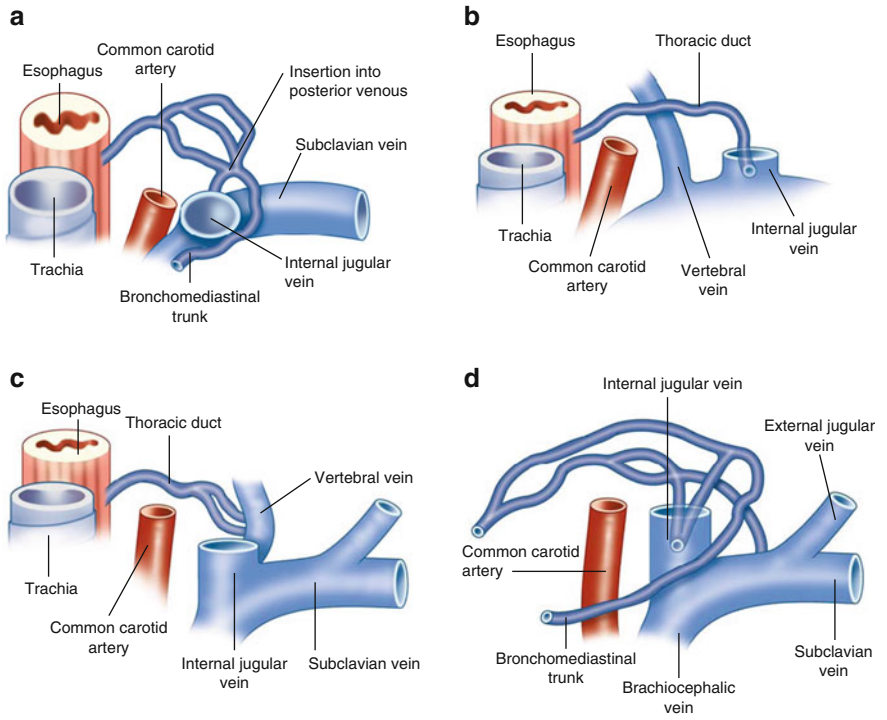

Fig. 3.2 Variations in termination of the thoracic duct. (**a**) Preterminal branching of thoracic duct and opening near the internal jugular vein. (**b**) A typical example of termination of thoracic duct into the internal jugular vein. (**c**) A bifid termination into the vertebral vein. (**d**) A complicated trifurcated termination draining into the internal jugular vein, subclavian vein, and lateral venous angle. The bronchomediastinal duct is also demonstrated (Redrawn from Langford et al. [28] and Reprinted with permission from Elsevier)

restrictive atrial septal defect, described the most severe spectrum of the lymphatic abnormalities. Graziono et al. [21] showed that four of the five patients with a restrictive ASD and hypoplastic left heart syndrome demonstrated moderate lymphatic dilatation and 1 patient had severe dilatation. In contrast, four of the five patients with nonrestrictive defects had normally lymphatics and one patient had mildly dilated lymphatics. The physiological explanation involves increased left atrial pressure in the fetal life which transmits to the pulmonary veins and the lymphatics, thus leading to the changes described above.

Cardiac Surgeries and Lymphatic Obstruction

Patients undergoing cardiac surgery often have morbidity and mortality related to pulmonary edema, impairment of normal respiratory function, and increased metabolic demands. Chylothorax is an additional cause of morbidity in patient

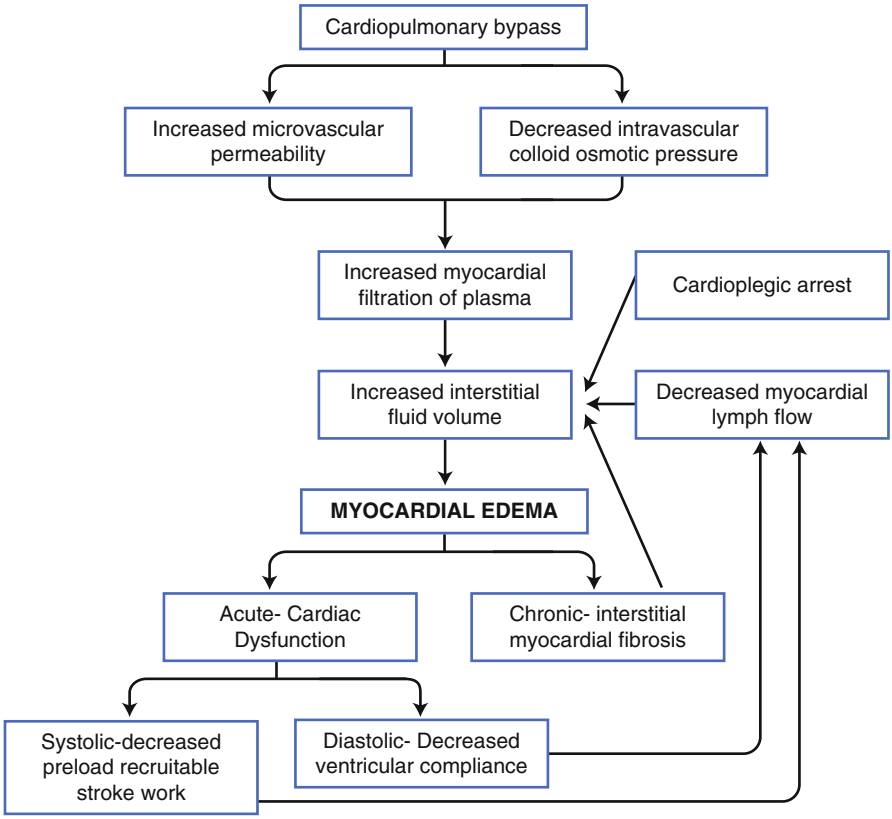

Fig. 3.3 Role of myocardial edema after cardiopulmonary bypass (Adapted from Nakamura and Rockson [38] by permission of Oxford University Press)

undergoing cardiac surgery [30]. It may be caused either by injury of the thoracic duct, increased pressure in the systemic veins exceeding that in the thoracic duct, or a central vein thrombosis.

Mehlhorn et al. [37] found that myocardial contraction is the major determinant of myocardial lymph flow and that impairment of such flow during cardioplegic arrest may contribute to postoperative myocardial edema and left ventricular dysfunction. As depicted in Fig. 3.3, cardiopulmonary bypass in children undergoing surgery for congenital heart disease leads to increased microvascular permeability and decreased intravascular colloid osmotic pressure. This results in increased myocardial filtration of the plasma thereby leading to myocardial edema. Myocardial edema thus causes systolic and diastolic dysfunction, further decreasing myocardial lymph flow and resulting in more myocardial edema [38]. As reliable means to detect myocardial edema in the clinical setting are not readily available at the bedside, many clinicians do not include this entity in their differential diagnosis of

cardiac dysfunction. Knowledge of the factors involved in myocardial fluid homeostasis may help to develop techniques minimizing myocardial edema formation and may lead to better therapeutic interventions [39].

Conduction Disturbances from Cardiac Lymph Flow Impairment

Anatomical studies have demonstrated the intimate relationship between lymphatic vessels and conduction structures in which a single longitudinal lymphatic pathway always runs parallel to the right bundle in animal studies. This suggests that cardiac lymph flow impairment could contribute to conduction disturbances and arrhythmia. Clinical studies have shown that lymphedema is associated with arrhythmia [40]. It has also been proposed that higher resistance in mediastinal lymphatics could be the cause of supraventricular tachycardia as these lymphatics are responsible for draining the atria.

Summary

In conclusion, the cardiac lymphatic system plays an important role in the pathophysiology and management of patients with congenital heart disease. Also there are significant lymphatic alterations in patients who have congenital heart disease, including left-to-right shunt lesions and left heart obstructive lesions. More efforts and research should be designed to utilize this knowledge of the cardiac lymphatic system for better healthcare management of children with congenital heart disease.

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