Lymphogenic cardiomyopathy

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Abstract

The lymphatic system plays a major role in the maintenance of cardiac function. Dysfunction of the cardiac lymphatics can lead to the onset of new pathology, aggravation of existing pathology or worsening of the long-term prognosis. Obstruction or severance of the principal trunks of the cardiac lymphatics results in phenotypic lymphogenic cardiomyopathy, which can manifest in a variety of ways, the most common of which is tachycardic or bradycardic arrhythmia. Localised tissue swelling resulting from lymphatic dysfunction (lymphoedema) disrupts the firing patterns of pacemaker cells within the sinoatrial and atrioventricular nodes, while also affecting the alignment of contractile proteins within myocytes. Some cases also demonstrate the presence of pericardial effusion; however, this is not thought to be causative of the arrhythmia and may indicate an advanced stage of disease. Removal of lymph from tissues limits the inflammatory response by removal or reduction of inflammatory mediators from the interstitium. In lymphostasis, inflammatory cells and metabolites accumulate causing localised tissue damage and fibrosis. This can lead to valvular stenosis or incompetence. The circulation of lymph also provides immune surveillance, therefore lymphostasis can increase the incidence (and severity) of infective pathologies such as myocarditis and endocarditis that may confound valvular pathologies. Cardiac lymphoedema produces changes on an electrocardiogram that mimic coronary ischaemia due to the effects of tissue oedema on the microcirculation of the myocardium. Arteriovenous shunting within the myocardium results in vessel-free areas that, unless rescued, will sclerose and eventually necrotise. This causes slow-developing alterations in ventricular function and plasma concentrations of hormones such as angiotensin-II and endothelin-I. This has implications in cardiac transplantation surgery as the principal lymphatic trunks are invariably dissected during this procedure. Restoration and monitoring of the function of these vessels may reduce the incidence of allograft failure, chylothorax and other post-operative complications, thereby improving patient prognosis. Understanding the various presentations of cardiac lymphatic disruption is important in identifying other pathological pathways that may intensify future cardiac pathologies if these presentations are not considered appropriately in the early stages of disease. This knowledge could open up alternative avenues of treatment that could be explored to prevent and improve the outcomes of the abovementioned cardiac pathologies.

For many years following its discovery, the lymphatic system was viewed as being of little importance in human bodily homeostasis. The first pioneers in the field of lymphatics research were heavily scrutinised and criticised for their efforts as many found their studies to be superfluous. Only recently have the lymphatics come to the forefront of medical research with their function in multi-system physiology and pathophysiology being demonstrated in experiments with animals (Kluge and Ullal, 1972).

The lymphatics make up a secondary vasculature system that works alongside the blood vasculature to remove fluid, proteins and cells (collectively known as lymph) from the interstitium of the tissues and through this regulates fluid homeostasis. Therefore most, but not all, vascularised tissues contain lymphatics. Further, the lymphatic system also plays an important role in immune surveillance and transport of nutrients such as dietary lipids from the intestine (Wang and Oliver, 2010).

In the heart, the lymphatic vessels can be separated into subdivisions that drain from the smallest into the largest vessels. The subendocardial plexus contains the smallest vessels, which drain into the myocardial plexus and then into the subepicardial plexus. Large vessels of the subepicardial plexus run parallel to the major coronary blood vessels within the atrioventricular and interventricular sulci. This dense network converges into larger vessels (normally one or two) containing valves that run anterior to the trachea and posterior to the pulmonary artery. They terminate at the cardiac node situated between the superior vena cava and brachiocephalic artery. Efferent channels from here then empty into the right lymphatic duct or the right angulus venosus (Johnson and Blake, 1966).

Although this is a common layout, several investigations into human cardiac lymphatic anatomy have demonstrated large variation in the lymph drainage pathways of the heart between individuals. This has implications in surgery as it limits the usefulness of standardised techniques to minimise the damage to the lymphatic vessels during surgical intervention.

The literature show a complex interaction between the cardiac lymphatics and cardiac pathology. In different situations this relationship can be unidirectional, bidirectional or circular/compounding in nature. This review will summarise these relationships using some of the key findings of the past.

Primary lymphatic pathology causing secondary cardiac pathology

Dysfunctional lymphatics in the periphery commonly manifest as peripheral lymphoedema causing localised tissue swelling that is characterised by pitting, a positive Stemmer sign (in the later stages), and abnormal drainage on a lymphoscintigram (Tiwari et al, 2003). Lymphatic dysfunction can also occur viscerally though this is much more difficult to diagnose. Lymphatic deficiency, removal, damage, blockage or poor functioning can result in lymphoedema. Lymphoedema can be classified in two ways: primary (i.e. hereditary or sporadic) or secondary (i.e. iatrogenic, tumour, trauma or infection related). Primary lymphoedema is most commonly caused by mutations of the vascular endothelial growth factor receptor-3 (*VEGFR-3*) gene, a protein involved in lymphangiogenesis (Ferrell et al, 1998; Karkkainen et al, 2000; Evans et al, 2003). In the general population, however, secondary causes of lymphoedema are most prevalent, with trauma and surgical removal of sentinel lymph nodes being the most common causes (Rockon, 2001). However, recent findings suggest most of these may have an underlying primary component.

Many case studies and research investigations have demonstrated a link between lymphatic impairment and cardiac arrhythmias. In industrialised countries, the source of impairment is most commonly extrinsic clamping or destruction of major lymphatic vessels during cardiac surgery (Rockon, 2001). Atrial fibrillation is a common complication seen in many patients following cardiac surgery. While the majority of these patients can be treated with commonplace antiarrhythmics such as beta-blockers, a distinct proportion of this population remain vulnerable to the sequelae of arrhythmia post-operatively despite having the same risk factors (Ak et al, 2005). The difference is related to the anatomy of the lymphatic system. Many major cardiac surgeries require distortion or removal of the aortic fat pad to access underlying coronary vessels; however, the lymphatic collector for the sinoatrial node resides in this tissue (Lupinski, 2009). Consequently, localised accumulation of lymph results in changes to the rhythmic firing pattern of the primary pacemaker node and subsequent morbidity associated with abnormal cardiac contractility.

While lymphatic-associated arrhythmias are most commonly seen post-surgery, they can also be related to intrinsic pathology such as lymphadenopathy. One such case study described the presence of atrial fibrillation in a man with concurrent tuberculosis and HIV infection (Mirica et al, 2012). In this case, computerised tomography and lymph node biopsy identified the presence of a lymphatic granulomatous mass causing left atrium deformation and resulting in abnormal rhythm generation. Treatment of the tuberculosis infection alleviated the cardiac symptoms. Another case from Germany described a patient presenting with palpitations (Abegunewardene et al, 2010). Investigations identified the presence of inguinal granulomatous lymphadenitis leading to the diagnosis of early sarcoidosis with cardiac involvement. Cardiac symptoms are only involved in up to 5% of cases of sarcoidosis; however, in these patients it has a large impact on mortality as heart failure, atrioventricular block and ventricular arrhythmias can ensue (Sekiguchi et al, 1996). Other electrical abnormalities associated with myocardial oedema include shortened atrial and ventricular refractory periods, increases in the sinus node recovery time, increases in the atrioventricular conduction time, ectopic beats and ventricular fibrillation (Gloviczki et al, 1983).

Within these cases, the presence of pericardial effusion was inconsistent suggesting that localised tissue swelling is sufficient to generate rhythm changes. It has been proposed that the changes in extracellular fluid ion concentrations in lymphoedematous myocardium may interfere with the conduction of the heart and consequently induce arrhythmia (Uhley et al, 1972). However, regional deformation of the pacemaker nodes alone may be sufficient to interfere with their function and result in abnormal firing patterns.

Impairment of cardiac lymph flow has been shown to cause myocarditis resulting in ventricular endocardial fibroelastosis. Autopsy findings from a middle-aged woman with a history of right-sided heart failure showed distended, ineffective lymphatic vessels with evidence of compensatory lymphangiogenesis, a thickened mitral valve, hypertrophic ventricles and a thick, diffuse endocardial fibroelastosis involving the entire left ventricle (Kilne et al, 1964). Microscopically, the myocardium was oedematous with multiple foci of acute muscle degeneration. In this case it is likely that localised tissue hypoxia from heart failure increased lymph flow initially, however, it resulted in endothelial damage and eventually impairment of lymph flow (Ullal, 1972). Subsequently, slow accumulation of inflammatory infiltrate caused low-grade myocarditis and generation of fibrous tissue within the ventricles thereby reducing their efficacy and contributing to the patient's demise.

Similarly, experiments with dogs have shown that surgically induced lymphostasis predisposes to staphylococcal endocarditis, myocarditis and recurrent rheumatic carditis (Miller et al, 1964). This study surmised that changes to valvular lymph flow perpetuate chronic inflammatory processes in the heart valves and myocardium by predisposing to inflammation, infection and fibrosis, resulting in establishment of a vicious cycle.

Further canine experiments have identified the effect of lymphatic occlusion on the microcirculation of the heart. Ligation of the major cardiac lymph trunks and regional cardiac lymph nodes produced changes on the ECG that mimicked cardiac ischaemia. Investigation into the patency of the microvasculature using ink injection revealed localised tissue oedema that had resulted in occlusion of capillaries and generation of arteriovenous shunts (Solti et al, 1981). Another group demonstrated that reductions in left ventricular function following lymphatic ligation correlated with increases in blood concentrations of angiotensin-II and endothelin-I (Wang et al, 2009). Taken together, the results discussed indicate that a combination of increased vascular resistance, reduced oxygenation, lymphoedematous myocardium, distorted contractile protein alignment, altered pacemaker node activity,

increased susceptibility to inflammatory and infective processes and a variety of other consequences of lymphatic failure may result in overall poor cardiac function and contribute significantly to allograft failure following cardiac transplantation (Ludwig et al, 1997; Kong et al, 2007).

Lymphatic involvement in the metabolic syndrome and abnormal fat deposition has been identified; however, the mechanisms remain unclear (Chakraboty et al, 2010). Adipose tissue is not only important for the storage and mobilisation of fats, it is also a powerful endocrine organ that releases pro-inflammatory mediators such as interleukin-6 and tumour necrosis factor alpha (Despres and Lemieux, 2006). Individuals with the metabolic syndrome are consequently predisposed to a chronic inflammatory atherogenic state that commonly leads to type 2 diabetes mellitus and atherosclerosis. The lymphatic system also plays a role in metabolic syndrome as it is important in modulation of immune function and inflammation as well as being largely responsible for the transport of lipids and cholesterol. In response to elevated blood triglycerides, the lymphatic system increases its flow rate to compensate. This phenomenon is referred to as the lymphogenic effect (Ee et al, 2000). In individuals with lymphatic impairment, this system fails causing ineffective lipid management and non-responsiveness to pro-inflammatory mediators. Lipids accumulate in the blood resulting in increased susceptibility to cardiac manifestations of hyperlipidaemia such as atherosclerosis. In addition, high concentrations of lipid in the odematous tissue surrounding the impaired lymphatic vessels can lead to abnormal fat deposition and reduced function of the surrounding organs (Warren et al, 2007).

Cardiac lymphatics and their role in prevention of cardiac pathology

Proper consideration of the cardiac lymphatics by gaining an appreciation of each individual patient's anatomical arrangement prior to surgery may decrease the incidence of poor post-operative outcomes and reduce morbidity and mortality associated with some higher-risk cardiac surgery. For example, in coronary artery bypass grafting, attempting to preserve the aortic fat pad may reduce the number of patients that have post-operative, lymphatic-related atrial fibrillation complications. Surgeons should also consider limiting the use of procedures that damage the major lymphatic vessels of the heart to those cases for whom alternatives are not available. One such example is the Fontan procedure that is used in patients with various forms of complicated congenital heart defects (Fredenberg et al, 2011). In this procedure, the pulmonary circulation is separated from the systemic circulation such that the blood from the inferior and superior venae cavae is directed into the pulmonary circulation rather than the heart. This procedure requires severance of the pulmonary trunk and closing of the pulmonary valve. Often, the two principle trunks of the cardiac lymphatics are transected during this procedure as they are commonly incorporated into the fascia of the pulmonary trunk. As a result, patient recovery is extended and susceptibility to various post-operative complications, such as infective endocarditis, is increased. As mentioned above, one common change seen in infective endocarditis is a local proliferation of lymph vessels surrounding the inflamed plaques. These new vessels may store fluid making the tissue largely oedematous and predisposes an individual to further valvular pathologies such as stenosis or regurgitation. Hence, blockade of VEGFR-3 and other molecules that stimulate lymphangiogenesis may inhibit the growth of these vessels and reduce lymphatic complications of endocarditis (Kholová et al, 2011).

In acute myocardial episodes, venous blood is often taken to assess oxygenation, lactate and a variety of other indicators that give clues as to the underlying pathology. Experiments comparing post-infarct lymph sampling to venous blood sampling indicated that lymph may be a much more useful indicator of anoxic changes in the local environment (Ullal, 1972). The study showed that lymph was a much more sensitive and accurate indicator of oxygenation, lactate and endothelial damage than was venous blood. Preceding investigations as a part of this study had shown that even after a very short cardiac arrest and sufficient resuscitation, the myocardium does not return to normal for quite some time, despite the blood results indicating otherwise (Ullal, 1972). Lymph on the other hand, was very sensitive to changes in the local environment and more closely resembled the status of the local myocardium. It is likely that the reason for this is the proximity to the myocardium as diffusion into the blood from tissues is less efficient than diffusion into the lymphatics.

Conclusion

In medicine today, the lymphatic system is still poorly understood despite the growing body of evidence suggesting its integral role in human bodily homeostasis. Simple attention to these delicate vessels during surgery may improve the prognosis for patients in both the short and long term, thereby reducing the number and duration of hospital stays and improving quality of life for the many individuals affected by heart disease. A greater appreciation of the relationship between lymph fluid and the status of surrounding tissues as compared with blood, may improve initial diagnostic accuracy and improve the efficacy of treatments offered. As well as this, knowledge of the cardiac lymphatic system offers alternative pathways for treatment in certain conditions that are known to be exacerbated by the presence of oedema.

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