INTRODUCTION

Since Rudbeck first described the existence of cardiopulmonary lymphatic vessels in 1653[1], research progress into the relationship between cardiopulmonary function and mediastinal lymph flow, has been hampered because of scarcity of relevant technology, and the important effect of mediastinal lymph flow is largely overlooked in most textbooks. Undoubtedly, the research progresses in this field critically rely on the techniques about cardiopulmonary functional analysis, animal models, and imaging system. Recent progresses in lymphatic vascular biology provide a new way to further explore the effect of mediastinal lymph flow[2].

In conventional point of view, lymphatic vascular system mediates tissue fluid homeostasis by providing an important route for fluid and protein transport, and plays a complementary role to the blood vessels in fluid reabsorption and tissue perfusion. The blood vessels deliver oxygen and nutrients, and carry away waste products for detoxification and replenishment; while the lymphatic vessels return the protein-rich exuded fluid to the bloodstream[3]. According to this conventional point of view, the consequence of lymph flow impairment merely refers to tissue edema other than specific tissue or organ injury.

Different from conventional view about lymph flow impairment which may cause tissue edema to a varying extent, mediastinal lymph flow impairment can bring a fatal consequence. Mediastinal lymph flow impairment may cause cardiopulmonary dysfunction by interrupting both the cardiac contraction manner of cardiomyocytes “asynchronized” contraction and pulmonary perivascular lymphatic remodeling.

Key words: Cardiac; Pulmonary; Lymph Flow; Lymphatics; Mediastinal
is direct dye injection and another is lymphatic specific molecular imaging\[16\]. However, direct dye injection method is only suitable for imaging “non-contracting” lymphatic vessels, and lymphatic specific molecular imaging method can be used for imaging both “contracting” and “non-contracting” lymphatic vessels. Using the dye injection technique, it was found that cardiac lymphatic vessels exist in various sites of the heart including the sub-endocardium, mid-myocardium, and sub-epicardium, and also in the atroventricular and semilunar valves in the mammalian heart. The cardiac lymphatic vessels exist in two forms comprising the lymphatic capillary plexus and the collecting lymphatic vessel. The lymphatic capillary plexus is seen in the mid-myocardium and sub-endocardium with the sub-endocardial lymphatic capillary plexus lying parallel to the surface of the endocardium. The collecting lymphatic vessels can be seen in the sub-epicardium; they unite into single or multiple lymphatic trunks and subsequently proceed to the mediastinal lymphatic vessels which include the right lymphatic duct and the thoracic duct[16-17]. Eventually, mediastinal lymphatic vessels merge into the subclavicular vein completing the lymph flow circulation. Intravascular valves are present in the lymphatic vessels of both cardiac collecting lymphatic vessels and the cardiac lymphatic capillary plexus except for the part of the sub-endocardial plexus that drains the longitudinal muscle columns of the left ventricle. Intravascular valves maintain lymph flow in one direction and are most numerous in the sub-epicardial collecting lymphatic vessels.

With regard to the cardiac lymph outflow pathway, it is known that cardiac lymph fluid may travel through both the right lymphatic duct and the thoracic duct before merging into the blood circulation. However, it still needs to be clarified whether the predominant cardiac lymph outflow pathway is the right lymphatic duct or the thoracic duct, although studies found that the connection between the right or left cardiac lymphatic trunk and the arch of the thoracic duct was present. Cardiac lymphatic trunks were rarely connected with the thoracic duct within the mediastinum, and connections with the arch of the thoracic duct were usually reached through the left anterior mediastinal lymph node chain. The left anterior mediastinal lymph node chain was often reached by the right efferent cardiac lymphatic trunk draining lymph fluid from the right ventricle at the level of the origin of the internal thoracic artery on the left thymus gland, while a left recurrent chain originating from the left superior bronchial nodes joined with the thoracic duct at the arch level. There was also a connection between the left superior bronchial nodes and the right paratracheal nodes. Interestingly, the right paratracheal nodes were always the first nodes joined by the left efferent cardiac lymphatic trunk draining the left ventricle. Studies showed that the efferent lymphatic vessels from the right paratracheal nodes merge mainly into the right lymphatic duct[16,17].

In terms of lymph flow, it is well accepted that both the active lymphatic pumping and passive lymphatic pumping exist in lymphatic vascular system, and that the active lymphatic pumping is generated by the active spontaneous contraction of lymphangions while the passive lymphatic pumping is not\[16-20\]. Because of a relatively low pulsatile rate of the active spontaneous contraction of lymphangions and limited capacity to drain large amount of lymph fluid\[21\], the active lymphatic pumping is not considered to play any role in propelling cardiac lymph flow. Apparently, the passive lymphatic pumping plays a major role in the cardiac lymph flow. However, the key point and debate exist in the pathway how the passive lymphatic pumping works.

For near ninety years, a theory proposed by Kampmeier was widely cited to explain how the passive pumping is generated within the heart. He hypothesized that during diastole, the pressure of the blood in the ventricles drives lymph from the sub-endocardial lymphatic vessels into the mid-myocardial lymphatic vessels. During systole, the contraction of the mid-myocardium forces the lymph from the mid-myocardial lymphatic vessels into the sub-epicardial lymphatic vessels; eventually, the pressure of the dilated heart against the pericardium towards the end of diastole drives the lymph from the sub-epicardial lymphatics into the main lymphatic trunk leaving the heart. In his hypothesis, the pericardium plays a key role in draining lymph fluid from the heart. However, there is no evidence showing that severe lymphedema can be induced in the heart after pericardium removal in either animal studies or human heart surgeries. On the other hand, it is important to know that if there is any force from the heart against the pericardium, the heart dilation is inevitable. Likewise, pericardium removal does not cause heart dilation at all. Therefore, it is reasonable to speculate that the force driving lymph flow through the sub-epicardial lymphatics does not come from cardiac dilation against the pericardium, and this situation produced a new concept of cardiac contraction manner of cardiomyocytes “asynchronized” contraction, proposed by Cui\[19,20\].

In Cui’s hypothesis, the driving force for cardiac lymph flow mainly comes from powerful sub-epicardial muscular contractions, and the lymph flow efficiency through the sub-epicardial lymphatic vessels depends on the power of cardiomyocytes “asynchronized” contraction. It is hypothesized that the three parts of the cardiac muscles, i.e., sub-endocardium, mid-myocardium, and sub-epicardium, are not committed to the same contraction simultaneously for efficient blood ejection and cardiac lymph flow. For example, during systole, the powerful contraction of the sub-endocardium and mid-myocardium contributes to blood ejection; however the sub-epicardium remains relaxed and is not committed to contraction simultaneously in order to collect lymph fluid from the layer of the mid-myocardium. During diastole, the sub-epicardium is committed to contraction to generate the driving force of lymph flow through squeezing the sub-epicardial lymphatic vessels and pumping cardiac lymph fluids from the heart. Although this contraction manner of the heart has been termed as cardiomyocytes “asynchronized” contraction, the terminology of cardiomyocytes “synchronized” contraction also has been used by Cui\[21\], because cardiomyocytes “asynchronized” contraction is precisely regulated in physiological condition.

**SELF-PROTECTIVE MECHANISM OF HEART**

Cardiomyocytes “asynchronized” contraction provides an important mechanism for blood perfusion into the cardiac walls. During systole, the blood enter into the layer of sub-epicardium due to its relaxation, and during diastole, the blood shall be squeezed into the layer of endocardium by the force of the sub-epicardial contraction. Therefore, it is the manner of cardiomyocytes “asynchronized” contraction rather than coronary artery pressure that shall play a key role in blood perfusion into the cardiac walls. As a matter of fact, a high level of coronary artery pressure is not required for blood perfusion into the heart in the condition of cardiomyocytes “asynchronized” contraction. This point of view is in part supported by the experimental findings that coronary blood flow does not change along with the increased coronary artery pressure, and remains a steady state in a wide range of coronary artery pressure\[22,23\]. Based on the manner of cardiomyocytes “asynchronized” contraction, the systolic myocardial volume is larger than the diastolic myocardial volume, and the value of the blood perfusion into the heart is equal to
Studies have shown that acute MLFI in animal models may cause severe sub-epicardial lymphedema with blistering of the epicardial surface, and scattered foci of sub-endocardial hemorrhage. While chronic MLFI in animal models may cause sub-endocardial hemorrhage in early stage, and decrease myocardial contractility and stroke volume. In addition, the ratio of dp/dt (maximal rate of increase of left ventricular pressure) to dp (pressure at the moment of maximal dp/dt) decreased after MLFI. Evidence also demonstrated that serum glutamic-oxaloacetic transaminase activity rose and electrocardiograms showed abnormalities after MLFI.

The above phenomena are interesting experimental findings which coincide with the manner of cardiomyocytes “asynchronized” contraction. In early stage of MLFI, lymphedema occurred in the layer of sub-epicardium. In order to drain lymph fluid out of the heart, the sub-epicardium had a reflex increase in the power of sub-epicardial contraction during diastole. And the excessive power of sub-epicardium blowed up blood vessels of sub-endocardium, and sub-endocardial hemorrhage occurred. However, chronic edema status interrupted the manner of cardiomyocytes “asynchronized” contraction, and weakened the cardiac contractility and decreased the stroke volume.

PULMONARY LYMPHATIC VESSELS AND LYMPH FLOW

There are two pulmonary lymphatic vascular systems, the subpleural and deep, that connect through the interlobular septa. Early investigators debated the origin of the deep lymphatic vessels, and electron microscopy has demonstrated a terminal and respiratory bronchiolar origin. However, Cui’s studies clearly showed that the deep lymphatic vessels mainly exist in the space around pulmonary blood vessels (so the deep lymphatic vessels also called perivascular lymphatic vessels in Cui’s terminology). In Cui’s animal studies, blocking mediastinal lymph flow may cause lymph accumulation in the perivasculare space other than elsewhere (as shown in Figure 1 and Figure 2). This is a very interesting finding for studying the mechanism of pulmonary blood vessel injury.

The pulmonary lymphatic vessels usually do not extend into the interalveolar septa. Pulmonary lymphatics eventually coalesce into large mediastinal lymphatic ducts, such as the right lymphatic duct and the thoracic duct. There has been some debate about the relative importance of the right lymphatic duct and thoracic ducts in pulmonary lymph drainage. Studies demonstrated that the fraction of lung lymph draining into the thoracic duct and right lymphatic duct can vary greatly among animals, however, on average, the right lymphatic duct and thoracic duct receive about equal fractions of the pulmonary lymph.

Pulmonary lymph flow originates mainly from perimicrovascular interstitial liquid. It is generally believed that lymph flow is determined mainly by the rate of microvascular filtration, and by the amount of fluid that has accumulated. Many factors promote pulmonary lymph flow, including the elevation of the left atrial pressure, increased bronchial arterial perfusion, hemodilution, increased cardiac output, and so on. In contrast, lymph flow may decline with the elevation of lymphatic outflow pressure; the effective resistance of the extrapulmonary part of the lymphatic system was larger than the resistance of the lymphatics in the lungs, and it may limit the maximal flow of lymph from edematous lungs.

CARDIAC INJURY BY MLFI

Studies have shown that acute MLFI in animal models may cause the difference between the systolic and diastolic myocardial volume (at this point, the volume of lymph fluid can be omissible because of small quantity). In addition to the above blood perfusion mechanism, the manner of cardiomyocytes “asynchronized” contraction provides an important mechanism of preventing heart from dilation, due to the sub-epicardial contraction during diastole. If all the myocardium contracts or relaxes simultaneously, the heart will dilate eventually because of repeated mechanical force towards ventricular walls from blood filling into the ventricles during diastole. A good cardiac performance requires good blood perfusion into ventricles and avoiding cardiac dilation, and the manner of cardiomyocytes “asynchronized” contraction wonderfully fulfills these prerequisites.
vessels exists around perivascular space rather than elsewhere in the lungs, and always proceeds along with pulmonary blood vessels. In physiological condition, the volume of lymph fluid around perivascular space is limited, the number of perivascular lymphatic vessels is numerous, and many of the perivascular lymphatic vessels maintain “collapsed” condition; while as the volume of lymph fluid increasing in the perivascular space, the lymphatic vessels around perivascular space undergo remodeling. The fashion of the perivascular lymphatic remodeling, is that various lymphatic vessels expand and lymphatic vascular walls coalesce with each other to form very limited number of lymphatic trunk(s), that lymphatic vascular permeability decreases dramatically to an extent that lymphatic trunk(s) enwrap the perivascular lymph fluid completely, and that perivascular lymphatic trunk(s) prevent blood vessel wall from direct contacting “toxic components” contained in the lymph fluids. Subsequently, as the volume of lymph fluids decreasing, the lymphatic trunk(s) change back into numerous lymphatic vessels with high lymphatic vascular permeability. This is an important mechanism for body to protect pulmonary blood vessels from injury. However, the capability of perivascular lymphatic remodeling is probably limited by the lymph volume accumulated in the perivascular space, and/or by both the number and function of the perivascular lymphatic vessels. Failure of perivascular lymphatic remodeling may cause blood vessel injury (as shown in Figure 3). In Cui’s studies, the failure of perivascular lymphatic remodeling occurred in the part of the lungs, not in the fashion of “all or none” of the entire lungs.

**PULMONARY INJURY BY MLFI**

In a rabbit model, Cui demonstrated that MLFI for 4 hours caused severe lymph fluid accumulation in the perivascular space in some segments of the lungs, and the lymph fluid is distributed along with pulmonary blood vessel sheath from small blood vessels to large blood vessels. There is no lymph fluid accumulation elsewhere. MLFI for 4 hours did not induce entire lung edema, but it may not exclude the possibility of pulmonary edema in a long-term MLFI. On the other hand, MLFI caused blood vessel endothelial injury in which histological examination showed endothelial cells bulged and vacuolized in some segments of the lungs, which is considered as the results of the failure of perivascular lymphatic remodeling in these segments.

In addition, MLFI for 4 hours caused a 4 ± 1 mmHg rise in pulmonary artery pressure, which is considered as the results of both perivascular lymph fluid accumulation and endothelial injury. Perivascular lymph fluid accumulation increased pulmonary vascular resistance and lowered vascular compliance. Therefore, MLFI may contribute to the occurrence of pulmonary hypertension.

**THE EFFECT OF IMPROVING MEDIASTINAL LYMPH FLOW**

Studies showed that improving mediastinal lymph flow may bring benefits to the heart and lungs. For example, in an animal model of myocardial ischemia or ischemia/ reperfusion, studies showed the beneficial effect of hyaluronidase on preventing cardiac injury by enhancing cardiac lymph flow. Also, in an animal model of myocardial infarction, studies showed that cardiac lymph flow decreased shortly after occlusion of the left anterior descending artery and cardiac lymphatic filling decreased in the infarct zone of the heart. However, hyaluronidase and CLS 2210 (a benzenesulfonate derivative) were found to prevent lymphatic occlusion and collapse, and significantly reduced the extent of myocardial injury from arterial occlusion.

**CONCLUSIONS**

Mediastinal lymph flow impairment may cause cardiopulmonary dysfunction by the mechanism of interrupting both the cardiac
contraction manner of cardiomyocytes “asynchronized” contraction and pulmonary perivascular lymphatic remodeling. And both the cardiac contraction manner of cardiomyocytes “asynchronized” contraction and pulmonary perivascular lymphatic remodeling, play a key role in maintaining normal cardiopulmonary function. On the other hand, establishing functional lymphangiogenesis for improving mediastinal lymph flow is a hot research area[7].

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CONFLICT OF INTERESTS

The author declares there is no conflict of interests.

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