



## Manner of Cardiomyocytes Asynchronized Contraction: A New Finding

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### Abstract

The manner of the cardiomyocytes asynchronized contraction is a new concept revealing the mechanism of the cardiac contraction manner in physiological condition. The manner of the cardiomyocytes asynchronized contraction refers to that during systole both the sub-endocardium and the mid-myocardium contract while the sub-epicardium relaxes, and during diastole both the sub-endocardium and the mid-myocardium relax while the sub-epicardium contracts in physiological condition. The interruption of the manner of the cardiomyocytes asynchronized contraction may cause various heart diseases, including but not limited to myocardial ischemia/infarction, heart failure, and ventricular arrhythmias. The underlying mechanism is explored. This current review summarizes all recent progresses in the research area of the manner of the cardiomyocytes asynchronized contraction.

**Keywords:** Cardiac contraction; Contraction manner; Asynchronized contraction; Cardiomyocytes contraction; Epicardial repolarization; Cardiomyocytes electrotonic coupling

### Introduction

The number of the patients with heart diseases is growing fast globally, and heart diseases have become the major diseases causing human death in many countries. Among various heart diseases, myocardial ischemia/infarction, heart failure, and ventricular arrhythmia are most common life-threatening diseases, and many efforts have been put on exploring the underlying mechanism and its therapy. Although numerous technologies have been developed last decades and applied on the therapy of the heart diseases, the result of the treatment is generally unsatisfactory [1], due to that the underlying mechanisms of many heart diseases remain unknown.

There is no doubt that knowing cardiac physiological phenotype correctly is the foundation for further exploring its molecular mechanisms, and is fundamentally important for exploring the pathogenesis and therapeutic strategy of the heart diseases. Without knowing the cardiac physiological phenotype, then the results of the research and therapeutic strategy become meaningless. With regard to the cardiac physiological phenotype of the cardiomyocytes contraction manner, it has been a law that the excitation-contraction in ventricles undergoes “all or nothing” fashion in physiological condition [2]. This conventional viewpoint about myocardial excitation-contraction in “all or nothing” fashion refers to that during systole all the ventricular cardiomyocytes contract simultaneously, and during diastole all the ventricular cardiomyocytes relax simultaneously. However, this conventional viewpoint about myocardial excitation-contraction in “all or nothing” fashion is unable to explain most cardiac events such as the mechanism of cardiac wall blood perfusion and the mechanism of cardiac dilation and so on, and in recent years challenged by a new theory of the cardiac contraction manner of the cardiomyocytes asynchronized contraction (CAC) [3-5].

The new theory of the cardiac contraction manner of the CAC, reveals that the whole ventricular cardiomyocytes do not undergo “all or nothing” excitation-contraction manner in physiological condition, but undergo asynchronized contraction. The ventricular myocardium is comprised of three layers, ie, sub-endocardium, mid-myocardium, and sub-epicardium. In physiological condition, the manner of the CAC refers to that during systole both the sub-endocardium and the mid-myocardium contract while the sub-epicardium relaxes, and during diastole both the sub-endocardium and the mid-myocardium relax while the sub-epicardium contracts. This new finding indicates that the cardiomyocytes between the sub-endocardium/mid-myocardium and the sub-epicardium behave differently, and the behavior of the cardiomyocytes between the sub-endocardium/mid-myocardium and the sub-epicardium is precisely regulated [4,5]. This current

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review summarizes all recent progresses in the research area of the manner of the CAC.

## Background of Manner of CAC

The concept of the manner of the CAC appears as the result of the research of the cardiac lymph outflow pathway [3-5]. It is well known that both the active lymphatic pumping and the passive lymphatic pumping exist in lymphatic vascular system. The active lymphatic pumping is generated by the active spontaneous contraction of the lymphangions and the passive lymphatic pumping is driven by surrounding tissue compression to the lymphatic vessels [6-8]. Because of a relatively low pulsatile rate of the active spontaneous contraction of the lymphangions and limited capacity to drain a large amount of lymph fluid [9,10], the active lymphatic pumping is not considered to play a role in propelling cardiac lymph outflow [3-5]. Apparently, the passive lymphatic pumping plays a major role in the cardiac lymph outflow. However, the key point exists in the pathway how the passive lymphatic pumping works.

In 1928, Kampmeier proposed a theory to explain how the passive pumping is generated in the heart [11]. Kampmeier 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 flow 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. According to Kampmeier's hypothesis, the pericardium is to play a key role in draining lymph fluid from the heart. However, there is no evidence to support Kampmeier's hypothesis because prominent lymphedema does not occur 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 in various settings. So, it is clear that the force driving cardiac lymph outflow through the sub-epicardial lymphatics does not come from the pressure of the dilated heart against the pericardium towards the end of diastole, and therefore efforts have been put on finding a new mechanism to explain the force driving cardiac lymph outflow through the sub-epicardial lymphatics, and recently a new concept of the cardiac contraction manner of the CAC has been proposed by Cui [3-5].

In Cui's research, the driving force for cardiac lymph outflow mainly comes from sub-epicardial muscular contractions, and the lymph outflow efficiency through the sub-epicardial lymphatic vessels depends on the power of the CAC. Cui hypothesized that the sub-endocardium, the mid-myocardium, and the sub-epicardium are not committed to the same contraction simultaneously for efficient blood ejection and cardiac lymph outflow. For example, during systole, the powerful contraction of both the sub-endocardium and the 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. And during diastole, the sub-epicardium is committed to contraction to generate the driving force of lymph outflow through squeezing the sub-epicardial lymphatic vessels and pumping cardiac lymph fluids leaving the heart [3-5]. These indicate that the manner of the CAC is precisely regulated by electrotonic coupling between

the sub-endocardial myocytes/mid-myocytes and the sub-epicardial myocytes. So the terminology of the cardiomyocytes synchronized contraction also was used by Cui [3].

## Cardiac Lymphatic Vessel and Lymph Flow

The existence of the cardiac lymphatic vessels was first reported over three centuries ago [12], but the research about the cardiac lymphatic vessels and its impact on the heart has been slow. The important effect of the cardiac lymph outflow on the heart had been poorly known until recently lots of knowledge and relevant technologies have gained impressive progresses [3-5,13-15]. By using the dye injection technique, it was found that the cardiac lymphatic vessels exist in various sites of the heart including sub-endocardium, mid-myocardium, sub-epicardium, and also in atroventricular and semilunar valves in mammalian heart [16-18]. The cardiac lymphatic vessels exist in two forms comprising the lymphatic capillary plexus and the collecting lymphatic vessels. The lymphatic capillary plexus are seen in the sub-endocardium and the mid-myocardium with the sub-endocardial lymphatic capillary plexus lying parallel to the surface of the endocardium. The collecting lymphatic vessels are seen in the sub-epicardium, and unite into single or multiple lymphatic trunks and subsequently proceed to mediastinal lymphatic vessels [19,20]. The mediastinal lymphatic vessels include the right lymphatic duct and the thoracic duct, which eventually merge into the subclavicular vein completing the lymph flow circulation. Intravascular valves are present in the lymphatic vessels of both the collecting lymphatic vessels and the cardiac lymphatic capillary plexus except for the part of the sub-endocardial capillary plexus that drain the longitudinal muscle columns of the left ventricle. Intravascular valves maintain lymph flow in one direction and are most numerous in the collecting lymphatic vessels.

As 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 is unclear whether the predominant cardiac lymph outflow pathway is the right lymphatic duct or the thoracic duct. In addition, studies have found that the connection between the right or left cardiac lymphatic trunk and the arch of the thoracic duct is present. Cardiac lymphatic trunks are rarely connected with the thoracic duct within the mediastinum, and the connections with the arch of the thoracic duct are usually reached through the left anterior mediastinal lymph node chain. The left anterior mediastinal lymph node chain is 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 joins with the thoracic duct at the arch level. There is also a connection between the left superior bronchial nodes and the right paratracheal nodes. Interestingly, the right paratracheal nodes are 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 [21,22]. With regard to the effect of the cardiac lymph outflow on the heart, studies have shown that acute cardiac lymph outflow impairment may cause severe sub-epicardial lymphedema with blistering of the epicardial surface, and scattered foci of sub-endocardial hemorrhage [23,24]. While chronic cardiac lymph outflow impairment in animal models may cause sub-endocardial hemorrhage in early stage, and decrease myocardial contractility and stroke volume [25-27]. In

addition, cardiac lymph outflow impairment decreases the ratio of  $dp/dt$  (maximal rate of increase of left ventricular pressure) to IP (pressure at the moment of maximal  $dp/dt$ ) [28-30]. Evidence also demonstrated that cardiac lymph outflow impairment increases the activities of serum glutamic-oxaloacetic acid transaminase and causes abnormal electrocardiograms [31]. In addition, lymph drainage from the atria may encounter much stronger resistance than that from the ventricles because of the weaker sub-epicardial muscular contraction in the atria than in the ventricles. Given the existence of high resistance in mediastinal lymph flow [32], lymph fluid retention is more likely to occur in the atria, often inducing supraventricular arrhythmias. This speculation is in part supported by clinical investigation [33,34]. In contrast, studies showed that improving cardiac lymph outflow may bring benefits to the heart. 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 outflow [35,36]. Also, in an animal model of myocardial infarction, studies showed that cardiac lymph outflow decreases shortly after occlusion of the left anterior descending artery and cardiac lymphatic filling decreases in the infarct zone of the heart. However, hyaluronidase and CLS 2210 (a benzenesulfonate derivative) are found to prevent lymphatic occlusion and collapse, and significantly reduce the extent of myocardial injury from arterial occlusion [37,38]. Improving cardiac lymph outflow by lymphangiogenesis is also an interesting research area [14].

## Manner of CAC

The heart is a highly efficient and self-protective organ. For maintaining persistent cardiac pumping function, the cardiac contraction manner must meet the prerequisites which include efficiently pumping lymph fluid out of the heart, efficient blood ejection out of the heart, sufficient blood perfusion into the cardiac walls, and effectively preventing cardiac dilation [3-5]. Firstly, the cardiomyocytes not only consume a large amount of nutrients and oxygen for active contraction, but also produce a large amount of "toxic" materials which is contained in lymph fluid. The accumulation of the "toxic" lymph fluid within the cardiac walls will directly harm to the cardiomyocytes, and particularly the cardiomyocytes electrotonic coupling between the sub-endocardium/mid-myocardium and the sub-epicardium, leading to injury to the cardiac performance. Thus, efficient lymph pumping is necessary in each cardiac contraction/relaxation cycle. Based on the evidence that the collecting lymphatic vessels are always located in the sub-epicardium, there is no doubt that cardiac wall lymph outflow direction is from endocardium to epicardium, and that the manner of the cardiomyocytes contraction must be good for draining lymph fluid from endocardium to epicardium subsequently leaving the heart. Secondly, efficient blood ejection out of the heart requires using both minimal number of cardiomyocytes and minimal oxygen consumption to pump blood out of the heart. The heart is a high efficient organ, and blood ejection out of the heart does not require all the ventricular cardiomyocytes to participate in the same contraction simultaneously. Thirdly, the cardiac contraction manner needs to ensure the blood-ejection cardiomyocytes to receive a plenty of blood supply in each cardiac contraction/relaxation cycle, because the blood-ejection cardiomyocytes consume a large amount of nutrients and oxygen for contraction. Finally, the cardiac contraction manner should prevent cardiac dilation. Blood filling into the ventricular chamber will bring pressure and tension to the blood-ejection cardiomyocytes, and it

will cause cardiac dilation and subsequently heart failure if there is no extra-mechanism to resolve the pressure and tension. Therefore, the cardiac contraction manner should have a mechanism to counteract the blood filling pressure and tension which are directed to the blood-ejection cardiomyocytes. Apparently, the cardiac contraction manner of the ventricular cardiomyocytes excitation-contraction in "all or nothing" fashion is unable to meet the above prerequisites. However, the manner of the CAC perfectly fulfills the above requirements. The manner of the CAC facilitates cardiac lymph outflow from endocardium to epicardium, and is prone to pumping lymph fluid leaving the heart. During systole, the blood pressure and the contraction of both the sub-endocardial myocytes and the mid-myocytes drive the lymph from both the sub-endocardium and the mid-myocardium into the sub-epicardium; and during diastole, the contraction of the sub-epicardial myocytes squeezes the sub-epicardial lymphatic vessels and pumps lymph fluid leaving the heart. The manner of the CAC is also an efficient way for blood ejection from the heart. The manner of the CAC only uses the cardiomyocytes located in the sub-endocardium and the mid-myocardium for blood ejection out of the heart, and the limited number of the blood-ejection cardiomyocytes decreases cardiac burden for oxygen demands. On the other hand, based on Laplace's law, cardiac wall tension is lowest in endocardium, and highest in epicardium. Therefore, the manner of the CAC demands oxygen and nutrients minimally for blood ejection. The manner of the CAC plays a key role in cardiac wall blood perfusion. During systole, the blood enter into the layer of the sub-epicardium along with the sub-epicardium relaxation, and during diastole, the blood get far into the layer of the mid-myocardium and the sub-endocardium by the force of the sub-epicardium contraction. On the other hand, the manner of the CAC changes cardiac wall geometry, which makes blood perfusion into the cardiac walls with larger blood volume and lower resistant way. Therefore, the systolic ventricular wall volume is larger than the diastolic ventricular wall volume, and the value of the blood perfusion into the heart is equal to the difference between the systolic and diastolic ventricular wall volume (at this point, the volume of the lymph fluid can be omissible because of its small quantity). As to the role of coronary artery blood pressure in cardiac wall blood perfusion, only a low level of coronary artery blood pressure is needed for maximal blood perfusion into the sub-epicardium during systole. This is in part supported by the experimental findings that coronary arterial blood flow remains a steady state within a wide range of coronary artery blood pressure, and that coronary arterial blood flow velocity is maximal at the end of systole and minimal at the end of diastole [39,40].

Furthermore, the manner of the CAC provides a perfect mechanism for preventing cardiac dilation. During diastole, the contraction of the sub-epicardium perfectly counteracts both the blood filling pressure and tension, which are directed to the sub-endocardium and the mid-myocardium. So, if there is no the contraction of the sub-epicardium during diastole, the cardiac dilation is inevitable. On the other hand, during diastole counteracting both the blood filling pressure and tension not only prevents cardiac dilation, but also makes the sub-endocardium and the mid-myocardium sufficiently relax, therefore, it further diminishes the oxygen demands of both the sub-endocardium and the mid-myocardium.

## Electrophysiological Characters of Cardiomyocytes

In the early 1990s, Researchers studied *in vitro* the three

electrophysiologically distinct cell types: sub-epicardial, “M”, and sub-endocardial myocytes. The “M” cells have longer action potential durations than the sub-epicardial and the sub-endocardial myocytes, and this difference increases along with prolongation of the electrical stimulation cycle length [41]. The ventricular sub-epicardium commonly displays action potentials with a prominent transient outward  $K^+$  current (Ito)-mediated notch (spike and dome) *in vitro* studies [42,43]. Although *in vitro* studies more likely construe intrinsic character of the individual cardiomyocytes, researchers found that there was little heterogeneity in action potential duration distribution across the free wall of the left ventricle in the intact heart [44-46]. This different result between *in vitro* and *in vivo* studies is likely caused by two reasons. One reason is that the cardiomyocytes *in vivo* and *in vitro* work differently, and another reason is that using current technology may be difficult to record the action potentials of the cardiomyocytes *in vivo* correctly. Researchers agreed that there exist pitfalls in the current recording methodology which is difficult in recording the cardiomyocytes action potentials *in vivo* [41]. Antzelevitch hypothesized that the presence of a prominent action potential notch in the sub-epicardium gives rise to a transmural voltage gradient between the “M” cells and the sub-epicardial cells during ventricular activation that manifests as a late delta wave following the QRS wave or what more commonly is referred to as a J wave. Also, Antzelevitch hypothesized that as the sub-epicardium repolarizes, the voltage gradient between the sub-epicardium and the “M” region continues to grow giving rise to the ascending limb of the T wave. The voltage gradient between the “M” region and the sub-epicardium reaches a peak when the sub-epicardium is fully repolarized - this marks the peak of the T wave [47]. Antzelevitch’s hypotheses have been unable to be confirmed and serious debate continues [48]. However, completely different from other researchers’ point of view, Cui hypothesized that in physiological condition QRS wave in electrocardiogram represents depolarization of the sub-endocardium and the mid-myocardium, and T wave in electrocardiogram represents re-depolarization from the nadir of the notch of the sub-epicardium during the course of sufficiently prolonged sub-epicardial repolarization in humans [5]. According to Cui’s research, in physiological condition, the action potential duration of the sub-epicardial myocytes may be sufficiently prolonged by electrotonic coupling with the mid-myocardium, and may manifest as biphasic pattern. The biphasic pattern of the action potentials of the sub-epicardial myocytes may be viewed as two action potential duration divided by the nadir of the sub-epicardial notch as the first spike phase and the second dome phase of the action potentials of the sub-epicardial myocytes. The first spike phase of the action potentials of the sub-epicardial myocytes may manifest as JT interval in electrocardiogram without the sub-epicardium contraction, and the second dome phase of the action potentials of the sub-epicardial myocytes may manifest as TJ interval in electrocardiogram with the sub-epicardium contraction. The depolarization during the first spike phase of the action potential duration of the sub-epicardial myocytes may inscribe J wave in electrocardiogram, and J wave is usually buried inside QRS wave in electrocardiogram and thus invisible in physiological condition. J wave may be visible in electrocardiogram when the J wave has a shift during the first spike phase of the action potential duration of the sub-epicardial myocytes in certain conditions such as hypothermia and so on. The re-depolarization from the nadir of the notch during the second dome phase of the action potential duration of the sub-epicardial myocytes inscribes T wave in electrocardiogram in humans. On the other hand, in physiological condition, the electrotonic coupling between the sub-

epicardium and the mid-myocardium is an important mechanism which may ensure the biphasic pattern of the action potentials of the sub-epicardial myocytes. Otherwise, uncoupling between the sub-epicardium and the mid-myocardium may show the action potential of the sub-epicardial myocytes as monophasic pattern (similar to that of the mid-myocytes) in which sufficiently prolonged sub-epicardial repolarization would vanish, the result of which may show various abnormality in electrocardiogram including flat T wave and so on. Importantly, the electrotonic coupling between the sub-epicardial myocytes and the mid-myocytes also ensures that the re-depolarization from the nadir of the notch during the second dome phase of the action potentials of the sub-epicardial myocytes always occur at near end of absolute refractory period of the mid-myocytes in order to avoid immediate depolarization of the mid-myocytes by the voltage from the sub-epicardial myocytes, and thus prevents ventricular arrhythmias. In experimental settings, the electrotonic coupling between the sub-epicardial myocytes and the mid-myocytes is probably susceptible to injury by invasive research approach, and the biphasic pattern of action potential duration of the sub-epicardial myocytes is probably difficult to be detected.

### Consequence of Interruption of CAC

The interruption of the manner of the CAC may cause serious heart damages. The interruption of the manner of the CAC mainly manifests as abnormal behavior of the sub-epicardium, which may bring about serious heart illness, such as myocardial ischemia/infarction, heart failure, and severe ventricular arrhythmias. The illness of the sub-endocardium and the mid-myocardium may be more likely induced by outside factors such as mediastinal lymph flow impairment [5], and seldom caused by themselves, the result of which damages the important electrotonic coupling between the mid-myocardium and the sub-epicardium. And thus the mid-myocardium loses precise control to the behavior of the sub-epicardium, and subsequently brings about various abnormality of the sub-epicardium. The abnormal behavior of the sub-epicardium manifests as either long lasting spasm during both systole and diastole, or contraction during systole without its diastolic contraction, or long lasting relaxation during both systole and diastole. Therefore, the abnormal behavior of the sub-epicardium either resists the blood to get into the heart or resists the blood distribution into the layer of the mid-myocardium and the sub-endocardium to a varying extent, causing heart ischemia or even myocardial infarction. Furthermore, the abnormal behavior of the sub-epicardium may also damage cardiac lymph outflow, and causes lymph accumulation within the cardiac walls. The excessive lymph accumulation in the low pressure region - epicardial perivascular space, also damages perivascular lymphatic vascular remodeling and subsequently causes epicardial coronary arterial endothelial injury [3-5,49,50]; together with the factors of significantly slow coronary arterial blood flow due to the interruption of the CAC, thrombosis is prone to occur in the epicardial coronary artery. On the other hand, electrotonic uncoupling between the mid-myocardium and the sub-epicardium, can make the voltage of the sub-epicardium likely trigger extra excitation-contraction to the mid-myocardium in certain conditions, and cause ventricular arrhythmias. It is not difficult to understand that the abnormal behavior of the sub-epicardium may cause cardiac dilation in certain circumstance, and directly lead to heart failure besides the cause of heart ischemia.

### Conclusion

The manner of the CAC plays a key role in maintaining

normal cardiac function. The whole ventricular cardiomyocytes do not undergo “all or nothing” excitation-contraction manner in physiological condition, but undergo asynchronized contraction. Physiologically, during systole the sub-endocardium and the mid-myocardium contract while the sub-epicardium relaxes, and during diastole the sub-endocardium and the mid-myocardium relax while the sub-epicardium contracts. The behavior of the cardiomyocytes between the sub-endocardium/mid-myocardium and the sub-epicardium is precisely regulated. The interruption of the manner of the CAC may cause various heart diseases, including but not limited to myocardial ischemia/infarction, heart failure, and ventricular arrhythmias.

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