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Medical Group

Journal of Cardiovascular Medicine and Cardiology

ISSN: 2455-2976 DOI CC By

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Dates: Received: 21 April, 2017; **Accepted:** 12 May, 2017; **Published:** 13 May, 2017

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Keywords: Coronary vein; Ligation; Cardiomyocyte; Auto phagosome; Angina

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Research Article

The Changes of Myocardium in Minipigs after Coronary Vein Ligation Observed by Transmission Electron Microscopy

Abstract

Background: The study of coronary artery disease has been quite thorough. But there is few study on coronary vein disease. In clinical practice, some patients have suspicious symptoms of coronary artery disease without any evidence of coronary artery spasm, but coronary angiography showed no obvious stenosis in coronary artery. It may have relationship to coronary venous dysfunction. This study aims to develop a coronary vein ligation model, to investigate the effect of coronary vein occlusion on myocardial cells in normal miniature pigs.

Methods: Adult minifies were divided into control group and intervention group. The coronary venous occlusion model was made by clamping the central vein. Myocardium was isolated from the myocardium and the myocardium was observed by transmission electron microscopy.

Results: There were no significant changes in the sham operation group (control group). Mitochondrial edema, cristae broken, hyperplasia and auto phage some appeared in the operation group (intervention group).

Conclusion: The ligation of the coronary vein causes dysfunction of myocardial cells. It gives us inspiration, coronary vein occlusive disease may be underestimated. It may be some causes of angina for patients with normal coronary angiography.

Introduction

Cell is a complete individual with complex structure, which can be used to carry out a variety of metabolic activities orderly, thus to complete a variety of physiological functions. At the same time, certain cell has adaptability to make different corresponding changes to different external stimuli. Particular, changes in the micro aspects affect cell function directly, thus to interrupt the affiliated organ's function, and eventually they are reflected to the whole-body level.

For so many years, due to the research development of coronary artery disease, studies on the effect of coronary ischemia and ischemia-reperfusion on myocardial cell micro level emerge in an endless stream. However, there are patients with normal coronary angiography without any evidence of coronary artery spasm, but angina symptoms [1-3]. Diagnosis with cardiac neurosis or microcirculatory disturbance remains insufficient [4]. There are research papers about coronary vein stenosis [5,6], especially, recent years, there were case reports about normal coronary angiography, but stenosis was found in coronary vein angiography [7].

Pathology and diseases of coronary sinus and veins are very rare [8,9]. They are most frequently mentioned with iatrogenic injury during mitral valve surgery or as a part of diffuse allograft vasculopathy after cardiac transplantation. Therefore, we doubt if there exists primary coronary venous disease. In this paper, we observed the micro-changes of myocardial cells after coronary vein ligation with transmission electron microscopy (TEM), aiming to explore the micro morphological and provide basic theoretical data for coronary vein stenosis and occlusive diseases.

Material and Methods

The experiments were performed in 6 male approximately 5 months' old Guizhou minifies with an initial average body weight of 20–30 kg. The investigation conformed to the Guide for the Care and Use of Laboratory Animals published by the

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U.S. National Institutes of Health [10], and the protocol was approved by the Institutional Animal Care Committee from Zhengzhou University People's Hospital, People's Republic of China. Pigs were divided into 2 groups: sham operation (n = 1), which was performed by opening the chest without coronary vein ligation (control group), and operation (n = 5), which was performed by opening the chest coronary vein ligation (intervention group).

Preoperative anesthesia, tracheal intubation and ventilator parameters

Pigs were intramuscular injected with diazepam (2mg/kg), atropine (0.06 ~ 0.08mg/kg) and ketamine (20mg/kg). And in 3 ~ 5 minutes, pigs stood instability and lay down, show that the successful induction of anesthesia. Anesthesia was maintained by 3% pentobarbital sodium. The ventilator was adjusted to the following parameters: 0.5L/min tidal volume, respiratory rate = 18/min, inhaled oxygen concentration (FiO2) =60%, inspiratory and expiratory time ratio = 1:2, positive end expiratory pressure (PEEP) = 0.49Kpa (5cm H2O) [11].

Coronary vein occlusion model

Sternotomy was performed on the sternum, up to the sternal notch, down to position 1 – 2 centimeters under the xiphoid tip. Eight to ten centimeters' longitudinal incision was made to expose the heart, then we cut the pericardium, and 7-O polypropylene suture was used to fix and suspend pericardium [12]. The coronary sinus was exposed to make clear the location of the middle cardiac vein. The middle cardiac vein proximal the coronary sinus was ligated in the intervention group with 7-O polypropylene suture. Pigs in the control group was dealt only with 7-O polypropylene suture encircled the middle cardiac vein.

Postoperative treatment

Necessary equipment and fixing fluid were prepared in advance, and was put in the refrigerator set for 4. Animals were sacrificed after 4-hour coronary vein ligation by intravenous injection of potassium chloride under anesthesia. And hearts were removed, and then middle cardiac veins and the myocardium nearby the middle cardiac vein was isolated. The tissues were rapidly washed with saline, put in the 2.5% glutaraldehyde solution on the plate coated with a fixed liquid wax, then cut into about 1 mm^3 cube or cuboid with a cross-section of about 1 mm^2 with double blade method. And then 2-3 small myocardium was taken into a fixed liquid bottle (marked with mark pen and sealed with medical tape) with a toothpick. Fixed with 1% osmium acid, small myocardium was dehydrated, mounted, ultramicrocut, electron stained, and observed under the TEM [13].

Result

1. TEM showed that, most of myocardial cells formed into bundles, fibers were with clear boundary, longitudinal showed obvious periodic stripes, every fiber was nearly parallel arranged with a few of weaves. There was no obvious abnormal change of myocardial ultrastructure, the muscle membrane was complete, the muscle fibers were arranged in order, sarcomeres were clear to identify, the mitochondrial lamellar structure was well preserved, the cristae were thin and dense (Figures 1A, 1B).

2. Compared with the control group (sham ligation), the heart muscle in the coronary vein ligation area of the intervention group was dark and edema. TEM showed that, some myocardial cells were edema, the muscle membrane were broken in different degree, the muscle fibers were arranged disorderly and some of them were with serious crack, sarcomeres were unclear to identify. And the cristae of mitochondria were edema and degenerated, and some were arranged disorderly or even with fracture. And some mitochondria were even vacuolization, hyperplasia. And autophagy emerged in some of the myocardial cells (Figures 2A-2E).

Discussion

Some cells have the characteristics of adaptation to the environment [14]. Deteriorated environment causes cell damage, even structural damage. In the intervention group, the emergence of autophagy and a series changes of mitochondria (edema, cristae broken, and hyperplasia) just showed that, the obstruction of venous reflux can cause the deterioration of

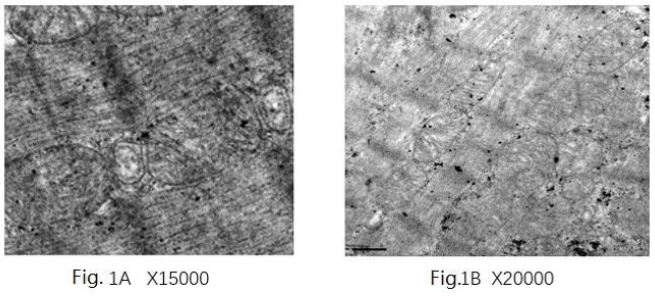

Figure 1: Myocardial cells formed into bundles, fibers were with clear boundary, longitudinal showed obvious periodic stripes, every fiber was nearly parallel arranged and the muscle fibers were arranged in order, sarcomeres were clear to identify.

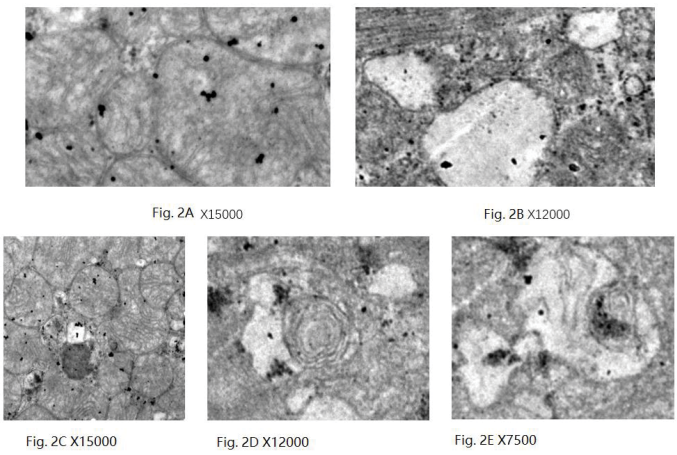

Figure 2: Myocardial cells appeared cristae broken (Figure 2A), edema (Figure 2B), hyperplasia (Figure 2C), and autophagy emerged in some of the myocardial cells (Figure 2D, Figure 2E).

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myocardial cells, may result from metabolic waste cannot be discharged. So that the heart function is affected, it may be the cause of angina like symptoms.

Results in the intervention group indicated that, it can lead to microscopic changes of myocardial cells with coronary vein occluded for 2 hours, similar to the changes caused by coronary artery ligation [15,16]. It may suggest that, coronary vein disease is likely to be some causes of angina pectoris.

However, there are studies showing that, the Coronary Sinus Reducer improves angina and ischemia by redistribution of blood from non-ischemic to ischemic myocardium [17]. There even are researchers holding the point of view, the implantation device in the coronary sinus can be used to treat refractory angina pectoris [18]. Obviously, the intervention for the coronary venous system has different mechanisms of angina with ours study. It may suggest that, a balanced blood supply for myocardium is necessary for the heart normal function.

In summary, the blood supply of heart consists of coronary artery and coronary vein. It may be not perfect for coronary artery disease to explain the mechanism of angina. There is few research involved in the disease of coronary venous system, our study is likely to provide some reference for it. However, given the lack of experimental samples and the limitation of technology, our conclusion is unconvincing, deeper and more perfect large-scale researches are needed. The diagnosis and treatment of angina may be transformed and improved in the future, because of the in-depth understanding for the mechanism of coronary vein disease.

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