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引發之心包黏連對急性心肌梗塞後左心室重塑之預防作用-動物實驗模式

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Prevention of left ventricular remodeling after acute myocardial infarction by induction of pericardial adhesion - A porcine model

引發之心包黏連對急性心肌梗塞後左心室重朔之預防作用 – 動物實驗模式

中文摘要

關鍵詞：急性心肌梗塞；心室重塑；心包膜粘連；心室拘限

急性心肌梗塞會導致左心室重塑，可影響左心室之梗塞部位及非梗塞部位。在心肌梗塞急性期，無法收縮之心室壁極易膨出，擴大，因而引發心室重塑。左心室重塑可導致臨床上之重要併發症，如心室瘤形成，急性期心臟破裂，再發心肌缺血，心律不整，以及心衰竭，結果是提早死亡。我們提出一個假說，在急性心肌梗塞發生後，若能儘速引發心包黏連以拘限左心室，使其不致擴大，應有可能防止心室重塑。為試驗此一假說，我們進行了本實驗。

共有 36 隻豬，七隻肉豬，29 隻迷你豬，進入本實驗，體重在 11 至 26 公斤。七隻肉豬於實驗引發心肌梗塞時有六隻死掉（85.7%），迷你豬則 29 隻中有七隻死掉（24.1%）。右冠狀動脈堵塞者 4 隻，3 隻死掉（75%），左前下行冠狀動脈及左迴旋冠狀動脈堵塞各有 16 隻及 13 隻,其死亡數分別為 3 隻(18.8%)及 7 隻(53.8%)。

有 3 隻豬並未在心包膜腔注射藥物，有 5 隻豬接受纖維蛋白膠注射，1 隻豬接受纖維蛋白膠及 Mitomycin C 4mg，5 隻豬接受 MMC 4mg，8 隻豬接受 MMC 6mg 心胞膜腔注射。接受心胞膜腔 MMC 注射的豬中有 2 隻發現有明顯心包膜黏連。病理檢查發現所有引發急性心肌梗塞豬其心臟重量均有明顯增加，但兩隻心胞膜粘連豬，其心臟重量之增加較不顯著。

總結之，由於在學習曲線上，我們在引發心肌梗塞時死亡率相當高，我們發現 LAD 堵塞之死亡率最低。此外引發心包膜粘連之成功率偏低，顯示應尋求更有效之方法，以引發心包膜粘連。

English abstract

Key words: acute myocardial infarction; ventricular remodeling; pericardial adhesion; ventricular containment.

Acute myocardial infarction (AMI) would proceed to left ventricular remodeling, involving both the infarcted and the noninfarcted segments of left ventricle (LV). During the acute phase of AMI, the noncontractile wall is most vulnerable to early infarct expansion, prior to scar formation. Ventricular dilatation and subsequent remodeling is more prone to occur in patients with large transmural infarctions. Left ventricular remodeling results in a high risk of clinical complications such as aneurysm formation, acute cardiac rupture, recurrent myocardial ischemic events, arrhythmias, and congestive heart failure, with consequent premature mortality in the patients with myocardial infarction. We proposal a hypothesis that soon after AMI, ventricular containment by induction of pericardial adhesion might prevent the process of ventricular remodeling through limiting the expansion and extension of infarct area. To test our hypothesis we performed this study.

A total of 36 pigs, 7 farm hogs and 29 mini pigs, were put into this experiment. The weight of the pigs was between 11 and 26 kgs. Among the 7 farm hogs, 6 (85.7%) died during the initial experiment when induction of AMI was attempted. For the mini pigs, 7 (24.1%) from 29 pigs died during the procedure. RCA was the coronary artery occluded in 4 pigs, 3 (75%) of them died during the procedure. LAD and LCX were the vessels intervened in 16 and 13 pigs, respectively, with mortality during the operation in 3 (18.8%) and 7 (53.8%) pigs, respectively.

On 3 pigs, chemical injection into pericardial sac was not performed. Fibrin glue injection into pericardial sac was performed on 5 pigs. One pig received injection with both fibrin glue and mitomycin C 4 mg. There were 5 pigs injected with 4 mg of mitomycin C and 8 pigs injected with 6 mg of that drug. There were 2 pigs with marked pericardial adhesion. Other pigs showed no pericardial adhesion. Pathological examination showed marked increase in heart weight in all experimental pigs in which AMI was induced. It seemed that the increase in heart weight was not so remarkable in the 2 pigs which showed pericardial adhesion.

It is concluded that in our experiment, due to the learning curve, we have high

mortality rate in the process of AMI induction. LAD occlusion would result in lowest mortality rate as comparing to RCA or LCX occlusion. Low success rate in the induction of pericardial adhesion indicates the need for refining the method of induction of pericardial adhesion.

Introduction

Soon after onset of acute myocardial infarction (AMI), the left ventricle (LV) changes in size, shape, and wall thickness (1). This process involves the infarcted as well as the noninfarcted portions of LV and these changes are collectively referred as ventricular remodeling (1,2). At the infarcted region, death of myocytes induces inflammatory response resulting in scar formation (1-3). The tensile strength of the affected region is transiently reduced during necrotic tissue resorption. During this period, the noncontractile wall is most vulnerable to the early structural deformation, known as infarct expansion, prior to scar formation (1,4). Ventricular dilatation with subsequent remodeling is found to occur in patients with large transmural infarctions, especially those with infarctions involving the apex of the ventricle (5,6). The apex is the thinnest region of LV with a large curvature. Loss of contractile function in this region results in immediate change in the regional curvature that would impose increased mechanical stress on this region to lead to infarct expansion (6).

Acute myocardial infarction also affects the region remote from the territory of coronary occlusion with increased relative shortening and greater end-diastolic lengths in these regions (7). These observations were reported in animal experiment models (7) as well as in humans (8). The combined changes in the infarcted zone and in the non-infarcted areas (i.e., left ventricular remodeling) would contribute to the later insidious dilatation of the left ventricle following myocardial infarction (9).

Left ventricular remodeling result in a greater risk of clinical complications such as aneurysm formation, cardiac rupture, recurrent myocardial ischemic events, arrhythmias, and congestive heart failure with subsequent premature death in patients suffered from myocardial infarction (4).

Some early interventions after myocardial infarction have been reported to limit the extent of myocardial damage and ventricular dilatation. Subsequent improvement in the severity of wall motion abnormalities and decreased chamber dilatation would result in reduction or abortion of ventricular remodeling (1,2). One of the well-known interventions is early use of angiotensin converting enzyme inhibitors (ACEI) after AMI. ACEI has been demonstrated to exert beneficial effects in preventing the occurrence of ventricular remodeling after AMI (10,11). Many large-scale clinical trials, examples are SAVE and AIRE, gave unequivocal evidences of benefits in using

ACEI after AMI (12-15). The beneficial effects of ACEI are multifold, including reduction of left ventricular filling pressure, inhibition of neurohormonal activation, and direct tropic actions on the myocytes and vascular cells.

In animal experiments, passive epicardial constraint using polyester mesh (Cardiac Support Device, CSD, Acorn Cardiovascular, Inc, St Paul, MN) has been demonstrated to prevent or even reverse ventricular remodeling in animals as well as in patients with heart failure (16-18). The results of clinical experience in using this device among 27 patients of heart failure was recently reported (19). This study demonstrated amelioration of symptoms and improvement in cardiac function in these patients. Yet, the drawback of this modality of treatment is the unavoidable surgical operation (sternotomy and pericardiotomy) to implant the mesh (19). Interestingly, in a clinical observation on 3 patients with cardiomyoplasty for severe heart failure, the improvement in heart size and symptoms was interpreted as mainly due to passive effects, i.e., external constraint with the resulted reversal of ventricular remodeling and less importantly due to systolic squeezing assist effect of the implanted striated muscle (20).

In recent years, the importance of ventricular remodeling in cardiovascular diseases, especially in coronary artery disease after myocardial infarction, hypertension and heart failure, has been well acknowledged and is under active research. But, up to date, mechanical constraint of left ventricle after myocardial infarction is still not successfully attempted.

Since adverse effects of changes in structure, hemodynamics and ventricular shape after AMI would soon progress to dilatation of the ventricle, any means which can prevent early dilatation of left ventricle after AMI would terminate or at least reduce the development and progression of ventricular remodeling. We, therefore, proposed an animal model to investigate the possibility of intervention on the development of remodeling process after AMI. In this model, a relatively non-invasive procedure with percutaneous approach to induce pericardial adhesion. Early development of pericardial adhesion would insert a containment effect on the heart which would limit the dilatation of the infracted left ventricle through a mechanical constraint force. We proposed that the containment effect of pericardial adhesion on left ventricle would prevent ventricular remodeling. This mechanical method of ventricular containment should be much more effective than the pharmacotherapeutic methods in the prevention of ventricular remodeling.

Subjects and Methods

A. Induction of acute myocardial infarction

Mini-pigs weighing 10-25 kg were used in the experiments. On the day of experiment, the pigs were fasting overnight. The pigs were anesthetized by intramuscular injection of ketamine 200-250 mg (4-5 ml, 50 mg/ml). The pigs were then intubated with a # 5 or #6 endotracheal tube and started with artificial respiration with room air. During the experiment, anesthesia was supplemented with intravenous diprivan injection and intravenous succinylcholine injection as necessary. Either right or left femoral artery was punctured using modified Selinger method or isolated by surgical cut-down. Under fluoroscopic guidance, a #6F right Judkins coronary catheter was advanced through femoral artery to engage one of the major coronary arteries (right coronary artery, RCA, left anterior descending artery, LAD, or left circumflex artery, LCX). The catheter was then carefully advanced deep to about the mid point of the catheterized coronary artery, sometimes helped with a 0.014" guidewire. Under fluoroscopy, a Gianturco coil of various diameters and lengths, according to vessel size and availability of the coils, was deployed through the catheter by using a 0.038" straight-tip guidewire as a pusher to induce thrombus formation in the coronary artery (21,22). Coronary angiography was performed 1-2 minutes after deployment of the occluding coil to check completeness of coronary occlusion. If coronary occlusion was not complete, another coils were deployed. During the procedure, ECG and blood pressure were continuously monitored. ECG was recorded before and after coronary artery occlusion. After the procedure, the pigs were cared with normal chow until subsequent experiment and sacrifice.

B. Induction of pericardial adhesion

Seven days after induction of AMI, pericardial adhesion was attempted by intra-pericardial injection of chemicals. The pigs were put on general anesthesia and artificial respiration as described above. In our initial proposal, we planned to use a particular pericardial access device (PerDUCER, Comedicus Inc., Columbia Heights,

MN) to access the pericardial space (23-27). But, due to unavailability of that product, we adapted other methods. Initially, we tried percutaneous injection method by using a Tuohy needle. Tuohy needle was connected to a bottle of normal saline hanged about 20 cm above the heart level. A small stab wound at the subxiphoid area was made. Through the stab wound, a Tuohy needle, with infusion flow open, was introduced into the skin and advanced, directing at about 45 degree over the horizontal level, toward the heart with intermittent fluoroscopic monitoring. When the infusion flow became fast suggesting entering a free chamber, the access of pericardial sac was checked under fluoroscopy by injecting half diluted contrast medium through the needle. If the pericardial sac was successfully accessed, pericardial injection for inducing pericardial adhesion followed.

Yet, after some trials, we found that pericardial access using this injection method was frequently difficult, sometimes fail and usually time-consuming. Later, we adapted a method of direct exposure of the pericardium through a minimal subxiphoid cut-down method. A wound with a length of about 5 cm over subxiphoid area was made to expose the pericardium. When pericardium was exposed, a #20 IV catheter was carefully introduced into the pericardial space. Through this catheter, pericardial injection to induce adhesion was carried out.

The materials we injected for inducing pericardial adhesion was also changed during our experiments. Initially, fibrin glue of a 3-fold dilution of fibrinogen (cryoprecipitate) was used (28). By doing so, 5 ml each of thrombin solution and cryoprecipitate fibrinogen and 5 ml of calcium chloride containing half diluted contrast medium were simultaneously injected through the catheter. After a few experiments, we observed no pericardial adhesion with injection of fibrinogen. We then started to inject mitomycin C, 4 or 6 mg in 4 ml of injection water, for inducing pericardial adhesion.

C. Measurements of physiological parameters

Through the experiments, pigs were put on ECG and blood pressure monitoring. Whenever, dangerous ventricular arrhythmias occurred, intravenous lidocaine injection was administered. Ventricular tachycardia and fibrillation were treated with DC cardioversion (200 joules). Other resuscitation medications were also adapted, such as atropine and adrenaline, whenever indicated. The pigs were injected with antibiotics

which included one dose of cephalosporin plus gentamycin and oral cephalosporin for one week. After procedure, the pigs were cared with normal chow. Follow-up ECG was taken at the time when the pigs were under procedure of pericardial injection. Body weight was measured at the occasions of initial experiment, pericardial injection and sacrifice.

D. Pathological examination

At sacrifice (4 weeks from induction of AMI and 3 weeks from induction of pericardial adhesion), the severity of pericardial adhesion was evaluated for the extent of involvement of adhesion and the thickness of the pericardium. The hearts were then removed. The areas of myocardial infarction were grossly observed and then the dimensions measured. The heart weight and measurements were also recorded.

Results

A. Basic characteristics of the experimental animals

A total of 36 pigs, 7 farm hogs and 29 mini pigs, were put into this experiment. The weight of the pigs was between 11 and 26 kgs. To access femoral artery for coronary occlusion, the method of direct puncture was performed on 4 pigs. For the remaining 32 pigs, cut-down at inguinal area was used to expose the femoral arteries.

Among the 7 farm hogs, 6 (85.7%) died during the initial experiment when induction of acute myocardial infarction was attempted. For the mini pigs, 7 (24.1%) from 29 pigs died during the procedure.

B. Induction of myocardial infarction

Three pigs died during catheterization before coil deployment. The remaining 33 pigs received coil implantation, 31 pigs with single coil deployment, 1 pig with 2 coils and the remaining pig with 3 coils implanted. RCA was the coronary artery occluded in 4 pigs, 3 (75%) of them died during the procedure. LAD and LCX were the vessels intervened in 16 and 13 pigs, respectively, with mortality during the operation in 3 (18.8%) and 7

(53.8%) pigs, respectively.

C. Induction of pericardial adhesion

To access pericardial sac for chemical injection, we adapted direct puncture method using Tuohy needle in 11 pigs and direct exposure by skin cut-down in 8 pigs.

On 3 pigs, chemical injection into pericardial sac was not performed. Fibrin glue injection into pericardial sac was performed on 5 pigs. One pig received injection with both fibrin glue and mitomycin C 4 mg. There were 5 pigs injected with 4 mg of mitomycin C and 8 pigs injected with 6 mg of that drug.

There were 2 pigs which were observed to have marked pericardial adhesion. First pig with marked pericardial adhesion was a pig (Pig #22) with body weight of 16.4 kg in which anterior wall myocardial infarction was induced by occlusion of the anterior descending coronary artery with a 3 x 20 mm coil. The heart weight of this pig was 195 g, with heart size of 8x8x4 cm. The infarction area involved anterior, lateral and apical area of left ventricle. The diameters of the infarct area were 3x2 cm. Another pig with pericardial adhesion was a pig with body weight of 18 kg and was occluded with coil (2x30 mm) implanted in right coronary artery. Infection of the subxiphoid cutdown wound was observed and pericardial adhesion was marked. The heart weighted 140 g, with dimensions measured 9x8x3 cm. The infarction involved posterior wall of the left ventricle with diameters of 3x4 cm. Left ventricle was measured 3x2 cm. Other pigs showed no pericardial adhesion.

D. Pathological findings

Totally 15 pigs were examined for pathological changes (Table 1). All hearts showed changes of myocardial infarction. There were 9 heart showed anterior/apical/septal infarction and 9 posterior/lateral/inferior infarction. The infarction sizes ranged from 1x0.8 cm to 4x3 cm. Adapting data from Hansard's study (29), we supposed normal heart weight for pigs is 0.55% of body weight, we found that the heart weight of the experimental pigs was much increased, observed 125.4 g, expected 87 g. In 2 pigs, there was pericardial adhesion observed: No. 6 and No.8 in Table 1. In Pig 6, the RCA was occluded and posterior infarction was produced with an infarction size of 4x3 cm. The

expected heart weight was 116.1 g and the observed heart weight was 160 g, an increase of 38%. In Pig #8, the LCX was occluded with a 2.5x1 cm postrior-lateral myocardial infarction produced. The expected heart weight was 77 g and the observed heart weight was 110 g, an increase of 43%.

Discussion

In our experiments, we proposed that pericardial adhesion would limit the expansion of the infracted area to reduced remodeling process after acute myocardial infarction. To the end of our experiments, we were not with great success in the induction of pericardial adhesion. We first tried fibrin gel by applying cryoprecipitate of human blood supplemented with thrombin and calcium gluconate. Yet, we found that this combination of coagulation materials seemed not worked well. Finally we tried mitomycin C injection, first we used 4 mg per pig and then increased to 6 mg per pig. We could induced pericardial adhesion in 2 of the 10 experimental pigs, quite a low success rate. It is difficult to reach a conclusion from such a small number of pigs which were successfully induced pericardial adhesion.

The future direction will be: 1) To find a more effective way to produce pericardial adhesion; 2) To induce myocardial infarction with more constant infarct site and size.

Conclusion

We are now established the pig model for inducing myocardial infarction. We are in some success in inducing pericardial adhesion. We need more experiments to confirm our hypothesis that pericardial adhesion soon after acute myocardial infarction may reduce the process of cardiac remodeling and improve cardiac function and prognosis of the patients.

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Table 1. Body weight, heart weight and infarction size of the experimental pigs

Pig #	Body weight	Heart weigtht	Expected	Infarction Site/Size

	(BW, kg)	(HW, g)	heart wt	
1	15.5	81.4	85.3	Ant / 2x1 cm
2	15.5	92.7	85.3	Ant / 2x2 cm
3	15.5	93.8	85.3	Lat-Apex /3x2 cm
4	16.8	104	92.4	Ant-Apex / 4x3 cm
5	12.8	100.4	70.4	Ant-Apex / 2x1.5 cm
6	12.2	100	67.1	Ant-Apex / 2.5x1 cm
7	14.4	88.2	79.2	Ant-Sep /1x0.8 cm
8	14.4	118	79.2	Ant-Apex / 4x3 cm
9	20	195	110	Ant-Apex /
10	15	140	82.5	Posterior /4x3 cm
11	21.2	160	116.1	Posterior / 4x3 cm
12	20	178	110	Lateral /2.5x2 cm
13	14	110	77	Post-Lat / 2.5x1 cm
14	14	160	77	Ant / 3x3 cm
15	16	160	88	Post-Lat / 3x0.5 cm