



Review article

Akt is a critical node of acute myocardial insulin resistance and cardiac dysfunction after cardiopulmonary bypass



Zhifa Wang^{a,b,1}, Yunya Wang^{c,1}, Yuehu Han^{a,1}, Qiang Yin^a, Sheng Hu^d, Ting Zhao^d, Tao Chen^e, Heng Ma^{f,*}, Chunhu Gu^{a,*}

^a Department of Cardiovascular Surgery, Xijing Hospital, Fourth Military Medical University, Xi'an 710032, Shaanxi, China

^b Department of Pediatrics, The Second Affiliated Hospital of Xi 'An Jiaotong University, Xi'an 710004, Shaanxi, China

^c Department of Nuclear Medicine, Xijing Hospital, Fourth Military Medical University, Xi'an 710032, Shaanxi, China

^d Department of Anesthesiology, Xijing Hospital, Fourth Military Medical University, Xi'an 710032, Shaanxi, China

^e Department of Cardiopulmonary Bypass, Xijing Hospital, Fourth Military Medical University, Xi'an 710032, Shaanxi, China

^f Department of Physiology, School of Basic Medical Sciences, Fourth Military Medical University, Xi'an 710032, Shaanxi, China

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ABSTRACT

Aims: Acute myocardial insulin resistance is an independent risk factor for patients who undergo cardiac surgery with cardiopulmonary bypass (CPB). However, the underlying mechanism of insulin resistance during CPB has not been fully investigated.

Materials and methods: To explore the role of myocardial insulin resistance on the cardiac function and its underlying mechanism, CPB operation and pharmacological intervention were applied in mini pigs, and myocardial insulin signaling, glucose uptake, ATP production and cardiac function were examined.

Key findings: Our data showed that CPB elicited not only hyperglycemia and hyperinsulinemia, but also inactivated Akt, and impaired the transposition of membrane glucose transporter-4 (GLUT-4), reduced glucose uptake and ATP production in the myocardium as well, which in turn was accompanied with cardiac dysfunction. Meanwhile, linear correlations were established among reduced myocardial glucose uptake, ATP production, and depressed cardiac systolic or diastolic function. Reactivation of Akt by SC79, an Akt agonist, partially alleviated myocardial insulin resistance and restored post CPB cardiac function via augmenting myocardial glucose uptake and ATP production.

Significance: These findings revealed that acute myocardial insulin resistance due to inactivation of Akt played a key role in cardiac dysfunction post CPB via suppressing glucose metabolism related energy supply.

1. Introduction

Cardiopulmonary bypass (CPB) is regarded as one of the most meaningful clinical advances during the last five decades. It maintains blood circulation and oxygen content of the body with a heart-lung machine, provides a bloodless surgical field with a comparably safe operation time for the surgeons to repair the most complex cardiac malformations. Despite major advances on CPB technologies, more attention still should be paid to the multiple insults during the operation [1,2], such as cardiac arrest, ischemia, non-pulsatile perfusion, hypotension, hemodilution, hypothermia, surgical trauma, hemorrhage, and so on, which thereafter trigger ischemia-reperfusion injury, systemic inflammation, multiple organ dysfunction, etc. [1,2]. Almost every patient experience postoperative cardiac dysfunction, CPB is the

leading contributor of mortality in hospitalized patients undergoing cardiac surgery [3].

Several clinical studies have reported high prevalence of hyperglycemia and hyperinsulinemia during and after CPB [4–6], which subsequently tightly associated with increased mortality as observed in cardiac surgery patients as well [7–10]. Moreover, a number of randomized controlled studies have demonstrated reduced mortality rates in the cardiac surgery subgroup by controlling the glycemic levels with intensive insulin therapy [11–13], and notably decreased the incidence of low cardiac output and of atrial fibrillation [7,11,14]. These findings suggested a possible connection between insulin resistance and postoperative cardiac dysfunction.

However, myocardial insulin resistant due to CPB has received very little attention. It was reported that cardiomyocytes in metabolic

* Corresponding authors.

E-mail addresses: hengma@fmmu.edu.cn (H. Ma), guchunhu@fmmu.edu.cn (C. Gu).

¹ These authors contributed equally to this work.

syndrome patients were more vulnerable to CPB as evidenced by severe postoperative cardiac fibrosis [15]. Gao et al. in his study revealed that CPB was accompanied with myocardial insulin resistance and glucose metabolism impairment [5,16,17]. But the underlying molecular mechanism of myocardial insulin resistance and the interaction with post CPB cardiac function alteration still remains unknown.

In this study, CPB operation and pharmacological intervention were applied in mini pigs to examine the myocardial insulin signaling, glucose metabolism, ATP production and cardiac function changes in order to clarify the existence of myocardial insulin resistance and the relationship with post CPB cardiac dysfunction, and also to explore the mechanism involved in it.

2. Materials and methods

2.1. Experimental animals

The experiment was performed according to the National Institutes of Health guidelines for the use of laboratory animals and was recognized by Fourth Military Medical University Committee of animal care. Eighteen adult male Bama mini-pigs, 8 months old, with an average weight of 22–26 kg (License No: SCXK (Su) 2011-0002, Taizhou, China) were randomly assigned into sham group, CPB group and CPB plus SC79 group ($n = 6$ in each group). Animals in sham group were cannulated without CPB, while those in CPB group were subjected to 150 min of CPB, as shown in Fig. 1A. In the CPB plus SC79 group, SC79 was injected intraperitoneally (40 mg/kg) at 30 min post aorta cross-clamp off.

2.2. CPB procedures

Chinese experimental mini pigs were fasted for 8 h and then were anesthetized with ketamine hydrochloride (20 mg/kg, intravenous injection, Beijing Chemical Reagent Company, Beijing, China) followed by a continuous infusion of propofol (0.15 mg/kg/min, I.V.). Endotracheal intubation was performed to acquire mechanical ventilation (volume 12–15 mL/kg, frequency 15 times/min) for the entire experiment. A dose of heparin (400 IU/kg, thousand red biochemical pharmaceutical, Changzhou, China) was injected into the right atrium for anticoagulation immediately after thoracotomy. Activated clotting time was stabilized at a value > 480 s during the operation. CPB was established after cannulation of ascending aorta, right atrium and postcava. CPB equipment included a disposable pediatric hollow fiber oxygenator (D400, Dideco, Mirandola, Italy), a roller pump inducing a non-pulsatile flow (BT600-2J, Zuofei, Shanghai, China), a hard-shell cardiomy reservoir (D754, Dideco, Mirandola, Italy), a bubble trap and an arterial blood filter. One liter of crystalloid solution (Delta Pharma, Pfarma, Germany) was primed to the extracorporeal perfusion circuit. A heat exchanger (BP50, PaiSite, Yang Zhou, China) was

performed for cooling and rewarming. Core temperature was continuously maintained at 30 °C and monitored by an esophageal temperature probe (JRD-D-II, RuiJi, Yancheng, China). The overall time of CPB was set at 150 min in each pig with non-pulsatile flow index of 2.4 to 2.7 L/min/m², and at about 60 mmHg of the mean systemic arterial pressure. After a perfusion of 30 min, ascending aorta was cross-clamped for 90 min, and cardiac arrest was achieved with an aortic root injection of cold (4 °C) St. Thomas cardioplegic solution (10 mL/kg) and maintained by once injection at every 30 min interval. Artery cannulation was inserted into left ventricular from left ventricular apex to record left ventricular end systolic pressure (LVSP) and left ventricular end diastolic pressure (LVEDP) by an electrophysiological recorder (RM6240, Chengdu, China). Blood and left ventricular myocardial samples were collected at pre AXC (0 min) and post-AXC (150, 180, 210 min), respectively (Fig. 1, A).

2.3. Biochemical assays

Plasma glucose was measured by glucose-oxidase photometric method (Dialab, Vienna, Austria). Plasma insulin was determined by chemiluminescent microparticle immunoassay on Architect i2000SR Analyzer (Abbott Laboratories, Abbott Park, IL, USA) following the manufacture's instruction. To exclude the influence of hemodilution, plasma insulin and glucose concentrations were normalized by haematocrit (Hct) dilution percentage using the following formula: Correction value = measured \times sample Hct/measured Hct [14]. The insulin resistance index (IRI) was calculated by HOMA-IR which was measured by using the formula of fasting insulin (mIU/L) \times fasting plasma glucose (mmol/l)/22.5 [18].

2.4. Measurement of cardiac glucose uptake by positron emission tomography/computed tomography

Electrocardiogram (ECG)-gated PET/CT imaging were performed one week before CPB and 210 min of post-AXC with a commercially available system (Symbia T2, Siemens, Germany). The animals were sedated with an intramuscular injection of ketamine and then 6.475 MBq/kg ¹⁸F-deoxyglucose (¹⁸F-FDG) was injected into the ear vein. CT images were acquired with 2-slice CT component of PET/CT scanner. Glucose uptake images were acquired 1 h after ¹⁸F-FDG injection using a dual-head camera with high-resolution collimators. Acquisition was continued for 10 min in list mode format. The dynamic PET was acquired for 30 min starting 1 h after i.v. injection of ¹⁸F-FDG. Images were reconstructed on a processing station (Syngo MI VA30A, Siemens, Germany). Glucose uptake in the myocardium was semi-quantitatively assessed by evaluating the standardized uptake value (SUV, activity concentration/injected dose/body weight). Regions of interest (ROI) were obtained by drawing the areas of equal size on the myocardium, and SUV was calculated from averaged image

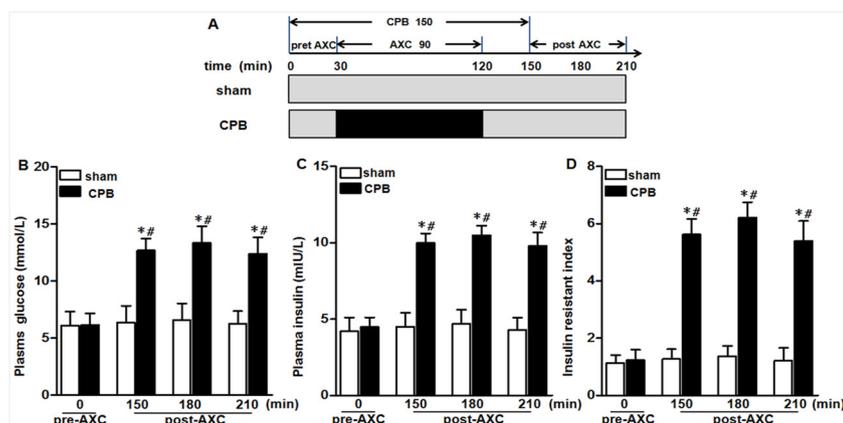


Fig. 1. Acute systemic insulin resistance after CPB.

A. Experimental protocol. Blood samples were collected at 0 and 150, 180 and 210 min from carotid artery;

B. Plasma glucose concentration;

C. Plasma insulin concentration;

D. Insulin resistance index as calculated by HOMA-IR formula.

* $P < 0.05$, v.s. that at pre AXC in sham group; # $P < 0.05$, v.s. that at the same time point of post CPB in sham group; $n = 6$ per group. CPB: cardiopulmonary bypass; AXC: aortic cross-clamp.

significantly dropped at all time points of post AXC in CPB group compared to those in sham group ($P < 0.05$, Fig. 2A). In order to confirm this finding, myocardial glucose uptake was further evaluated by PET/CT using ^{18}F -FDG. Myocardial ^{18}F -FDG accumulation was markedly attenuated at 210 min of post AXC in CPB group compared with that in sham group ($P < 0.05$, Fig. 2, B and C). Moreover, insulin (10 U/kg, i.p., 20 min before detection) produced a robust increase of ^{18}F -FDG accumulation at pre-AXC in the heart of both the groups ($P < 0.05$, Fig. 2, B and C), but failed to induce myocardial ^{18}F -FDG accumulation at 210 min of post AXC in CPB group, which was demonstrated by the lower SUV_{max} values compared with that in sham group ($P < 0.05$, Fig. 2, B and C). These findings suggested that CPB not only possessed an inhibitory effect on myocardial glucose uptake, but also blunted the insulin induced myocardial glucose uptake.

3.3. Impaired glucose uptake and reduced myocardial ATP production were tightly associated with post CPB cardiac dysfunction

Glucose is an import source of cardiac energy substrate for the functioning of heart, it is necessary to detect myocardial ATP content and cardiac function, and the relationship among them was also explored. Our findings illustrated that cardiac ATP content was decreased significantly at all time points post AXC in CPB group compared to sham group ($P < 0.05$, Fig. 3, A), which was positively correlated with myocardial glucose uptake (Fig. 3, D). Moreover, LVSP was dropped and LVEDP was elevated significantly at all time points of post AXC in CPB group compared to sham group ($P < 0.05$, Fig. 3, B and D), which indicating attenuated cardiac systolic and diastolic functions after CPB. The degree of post CPB cardiac dysfunction was closely correlated with

the reduction of myocardial ATP content (Fig. 3, E and F). These findings suggested an inhibitory effect of CPB on myocardial glucose uptake, which contributed to the reduced cardiac ATP content, leading to post CPB cardiac dysfunction.

3.4. Inactivation of myocardial Akt admitted blunted myocardial glucose transporter-4 translocation after CPB

To further explore the underlying molecular mechanism of impaired myocardial glucose uptake after CPB, insulin signaling cascade and myocardial glucose transporter-4 (GLUT-4) were examined. Insulin provoked the phosphorylation of insulin receptor, insulin receptor substrate, PI3K in both sham and CPB groups (Fig. 4, A–D). But less Akt phosphorylation and reduced Akt kinase activity were observed in CPB group compared to sham group ($P < 0.05$, Fig. 4, A, E and F). Myocardial membrane GLUT-4 is mainly responsible for insulin or contraction-mediated glucose transport via the activation of PI3K and Akt [22]. Accordingly, our data indicated that myocardial membrane GLUT-4 content was markedly elevated after insulin stimulation in sham group, but not in CPB group ($P < 0.05$, Fig. 4, A, G and H). These findings implied that inactivation of myocardial Akt after CPB resulted in the blunted GLUT-4 translocation.

3.5. Reactivation of Akt improved post CPB cardiac function via increased cardiac glucose uptake and ATP production

To further explore the role of Akt in post CPB myocardial impairment of glucose uptake, ATP production and cardiac function, Akt agonist SC79 was delivered at 30 min after aorta cross-clamp off. As

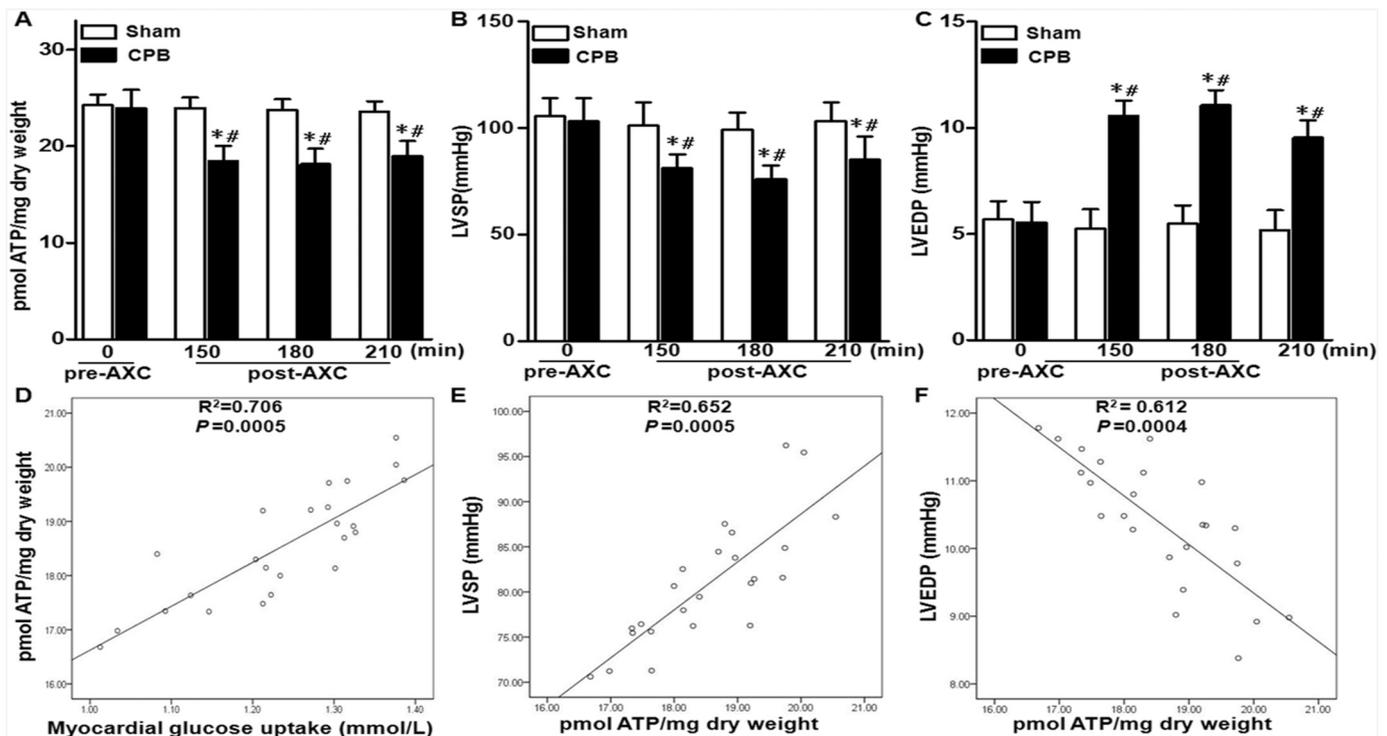


Fig. 3. Reduced myocardial ATP production and cardiac function was associated with declined glucose uptake.

- A. Myocardial ATP production.
 B. Left ventricular systolic function.
 C. Left ventricular diastolic function.
 D. Correlation of myocardial glucose uptake and ATP production.
 E. Correlation of myocardial ATP production and left ventricular systolic function.
 F. Correlation of myocardial ATP production and left ventricular diastolic function.

* $P < 0.05$, v.s. that at pre AXC in sham group; # $P < 0.05$, v.s. that at the same time point of post CPB in sham group; $n = 6$ per group. CPB: cardiopulmonary bypass; AXC: aortic cross-clamp; LVSP: left ventricular systolic pressure; LVEDP: left ventricular end diastolic pressure.

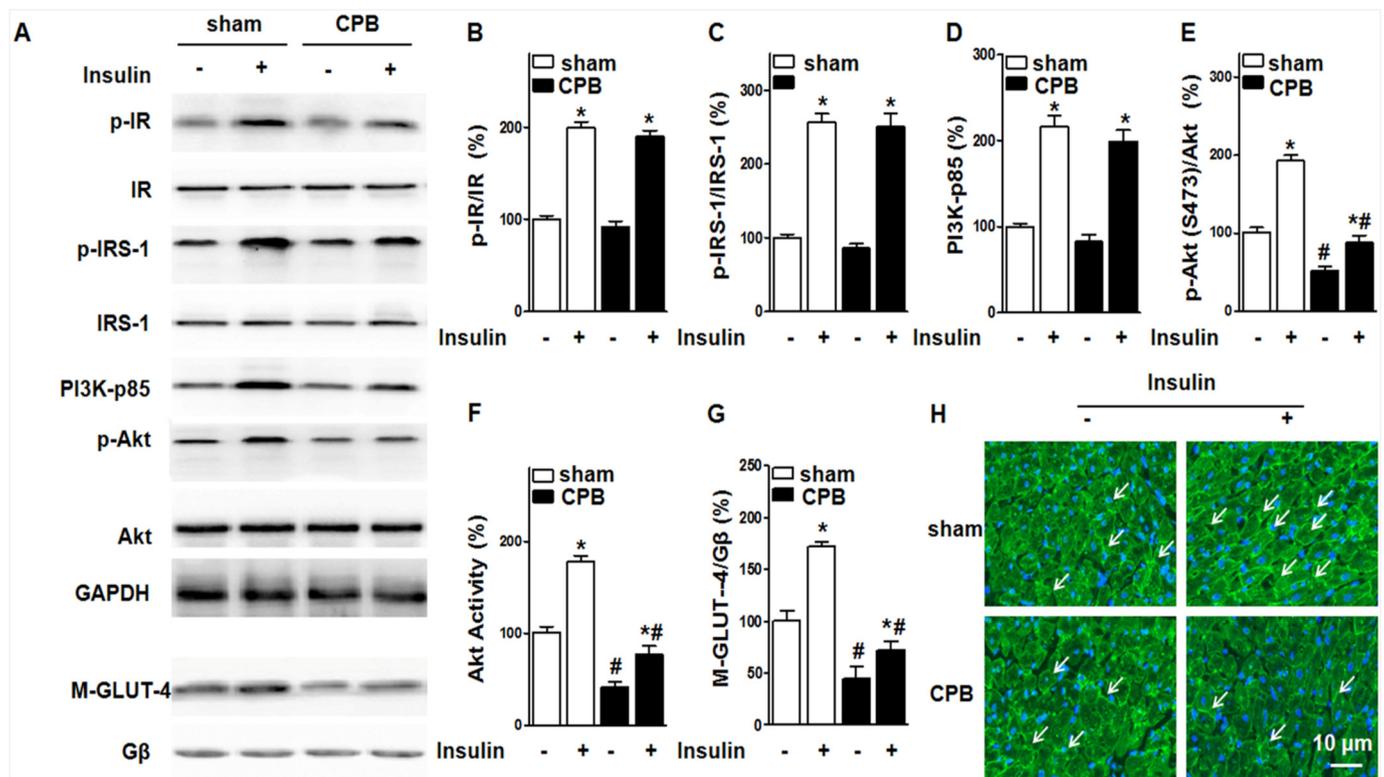


Fig. 4. Inactivation of myocardial Akt admitted blunted myocardial membrane glucose transporter-4 translocation after CPB.

A. Representative western blots of myocardial insulin signaling and membrane GLUT-4.

B–E and G. Quantification of bar graphs of myocardial insulin signaling and membrane GLUT-4.

F. Myocardial Akt activity.

H. Representative immunofluorescence of cardiac GLUT-4. White arrows indicate positive immunostaining.

Samples were collected at 210 min after AXC for these experiments. * $P < 0.05$, v.s. that in the sham or CPB group with saline treatment; # $P < 0.05$, v.s. that in sham or CPB group with saline or insulin treatment (0.075 U/kg); $n = 6$ per group. CPB: cardiopulmonary bypass; p: phosphorylated; IR: insulin receptor; IRS-1: insulin receptor substrate-1; GAPDH: glyceraldehyde phosphate dehydrogenase; M-GLUT-4: membrane glucose transporter-4.

shown in Fig. 5, A–D, SC79 treatment significantly increased both phosphorylated Akt and membrane GLUT-4 content ($P < 0.05$) compared to CPB group. Meanwhile, myocardial glucose uptake and ATP supply were increased after SC79 treatment ($P < 0.05$, Fig. 5, E–G). Consequently, cardiac dysfunction post CPB was significantly reversed after SC79 treatment compared to CPB group, as evidenced by the increased LVSP and decreased LVEDP ($P < 0.05$, Fig. 5, H and I). Hence, pharmacological activation of Akt after CPB was proved to be beneficial in improving the cardiac function via elevated myocardial glucose uptake and ATP production.

4. Discussion

Despite major advances last decades in the technology and medication applied during CPB for the prevention of side effects, a high prevalence of cardiac dysfunction post-CPB still existed and is positively correlated with mortality in hospitalized patients undergoing open heart surgery (cardiovascular surgery with CPB) [2,3]. In present study, we have demonstrated that acute myocardial insulin resistance was partly responsible for post CPB cardiac dysfunction. The detailed molecular mechanism underlying the post CPB cardiac dysfunction includes blunting of myocardial membrane GLUT-4 transportation by acute myocardial insulin resistance via inactivation of Akt. These mechanisms in turn results in the impairment of myocardial glucose uptake, insufficient ATP supply, and thereafter post CPB cardiac dysfunction. This was further validated by the linear correlation among myocardial glucose uptake, ATP production and cardiac function after CPB. Pharmacological activation of Akt by SC79 treatment alleviated acute myocardial insulin resistance after CPB, increased membrane

GLUT-4, myocardial glucose uptake and ATP production, and thus ameliorated post CPB cardiac dysfunction.

Since invented in 1953, the technology of CPB has been vastly ameliorated and currently majority of the patients were able to well tolerate the procedures. However, inevitably multiple severe insults, such as systemic inflammation and hypotension, non-pulsatile perfusion, stress response, coagulation disturbance, body temperature rise and fall, hemodilution, hyperinsulinemia and hyperglycemia, mechanical trauma, etc. still exist [5,6,14,23]. Previous studies demonstrate that cardiac dysfunction caused by CPB was positively correlated with increased morbidity and mortality in patients undergoing cardiac surgery [24,25].

The exact mechanism of cardiac dysfunction post CPB is still somewhat controversial. Some believe that CPB lead to a severe systemic inflammatory response, resulting in myocardial injury and cardiac dysfunction [5]. For years, multiple strategies have been explored to regulate and minimize the side effects of inflammation, which include optimized design of the mechanics, rational pharmacological interventions, utilize miniaturized CPB circuits, use of leukocyte filters, etc. [26–29].

However, study by Augoustides JG observed a little effect on cardiac dysfunction by suppression inflammatory response [30], although morbidity seemed to be low. Some believe that hyperglycemia during CPB is an independent risk factor for myocardial damage and cardiac dysfunction in patients undergoing cardiac surgery [31]. It is possible to ameliorate hyperglycemia through removal of glucose in the priming fluid by ultrafiltration followed by the addition of a balanced electrolyte solution [32]. However, a previous study observed little effect of “balanced ultrafiltration” on cardiac dysfunction, although there was a

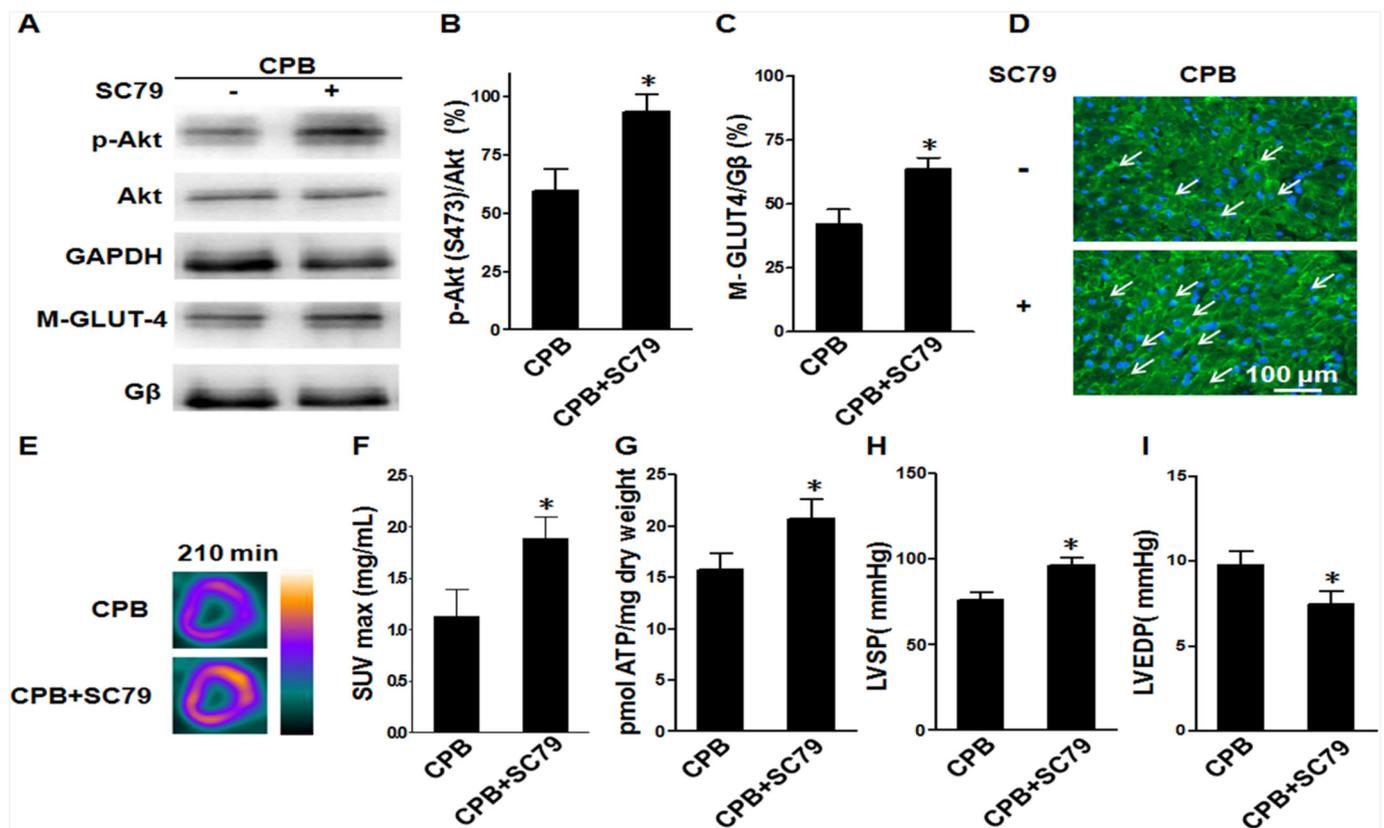


Fig. 5. Reactivation of Akt improved post CPB cardiac function via increased cardiac glucose uptake and ATP production.

A. Representative western blots of myocardial Akt and membrane GLUT-4 with or without SC79 treatment after 30 min of aorta cross-clamp off.

B and C. Quantification bar graphs of myocardial Akt and membrane GLUT-4 with or without SC79 treatment.

D. Representative immunofluorescence of myocardial membrane GLUT-4 with or without SC79 treatment. White arrows indicate positive immunostaining.

E. Myocardial glucose uptake evaluated by positron emission tomography/computed tomography (PET/CT) using ^{18}F -FDG with or without SC79 treatment at 210 min of post AXC.

F. Statistics of myocardial glucose uptake by PET/CT. Data were expressed as SUV_{max} .

G. Myocardial ATP production.

H. Left ventricular systolic function.

I. Left ventricular diastolic function.

Samples were collected at 210 min after AXC for these experiments. $*P < 0.05$, vs. that in CPB group; $n = 6$ per group. CPB: cardiopulmonary bypass; p: phosphorylated; GAPDH: glyceraldehyde phosphate dehydrogenase; M-GLUT-4: membrane glucose transporter-4; AXC: aortic cross-clamp; SUV_{max} : maximal standardized uptake value; LVSP: left ventricular systolic pressure; LVEDP: left ventricular end diastolic pressure.

decreased cardiac inflammatory factor and lactate concentration [33].

Furthermore, there are people who think that the molecular mechanisms of cardiac dysfunction after CPB include deficiency of cellular metabolites during cardiac arrest, and interstitial and intracellular edema, intracellular calcium overload [2,34], oxidative stress [35,36] post CPB. The main focus of previous studies on myocardial protection during open heart surgery is the precise ingredients of ideal cardioplegic solutions, which induce metabolic arrest, and maintains an appropriate metabolic environment (preventing the loss of cellular metabolites, providing metabolic material, include fructose, phosphocreatine, oxygen and other substrates, and preventing interstitial and intracellular edema). A large number of researches have demonstrated that the comparison of different compositions of cardioplegic solutions and different administration techniques (single vs. intermittent vs. continuous; antegrade, retrograde, or combined) to explore a way to reduce post-cardiac dysfunction after CPB [37–41] []. Despite all the efforts, post-CPB myocardial dysfunction still exists, so it is important to recognize that this impairment represents a complex mechanism that cannot simply be resolved by modulating myocardial metabolism during cardiac arrest and by adapting the ingredient of cardioplegic solution [2]. So, are there any other more important factors we have neglected that contributed to post CPB cardiac

dysfunction? In present study, we further explored the molecular mechanism of myocardial insulin resistance. Our results showed that the inactivation of Akt exhibited even at 30 min after aortic cross-clamp off in the myocardium of CPB group, which thereafter blunted the translocation of GLUT-4, and insulin stimulated glucose uptake. These findings provided direct evidence of acute myocardial insulin resistance may contribute to post CPB cardiac dysfunction.

It has been well recognized that the role of perioperative insulin resistance in the prognosis of patients undergoing cardiac surgery cannot be ignored, which is tightly correlated with postoperative cardiac dysfunction [6,10,42]. In accordance with this, our data represented overt decline in the cardiac function as evidenced by decreased LVSP and elevated LVEDP shortly after the surgery. Recording pressure-volume data could better isolate the contribution of preload vs. myocardial contractility on cardiac function. The validity of such analysis is dependent on a rapid and accurate measurement of LV volume and pressure simultaneously. The defect, in this article, there is no record measured Pressure-volume relationships, we will adopt the Pressure-volume relationships in our future study. Clinical and animal studies have demonstrated that myocardial insulin resistance inducing impairment of glucose utilization is one of the primary causes of cardiac dysfunction after myocardial ischemia reperfusion [43,44]. Since CPB

procedure per se is an artificially introduced ischemia and reperfusion process, and could be speculated that myocardial insulin resistance might play an important role in cardiac dysfunction after CPB. As mentioned, decreased myocardial glucose uptake due to reduced transmembrane translocation of GLUT-4 occurred shortly after CPB, which in turn resulted in the insufficient production of myocardial ATP. Moreover, there was a linear correlation between reduced myocardial ATP production and the degree of cardiac dysfunction in CPB group. Therefore, a clear relation was established that acute myocardial insulin resistance elicited a blunt in the uptake of cardiac glucose, resulted in cardiac dysfunction due to insufficient ATP production after CPB.

Indeed, the balance between energy supply and the energy utilization, while maintaining the normal function of all other organs has allowed the organism to improve the protection ability and prevent against ischemia-reperfusion injury and systemic inflammatory response, and most importantly eliminate the complications and mortality. Fatty acids is the major substrates utilized by the myocardium, and glucose accounts for about 20–30% ATP production in healthy adult heart, but the mechanism is different in reperfusion after myocardial infarction [45,46]. Uptake and oxidation of carbohydrates was reported to be increased during the immediate reperfusion phase following myocardial infarction [47]. Numerous studies have shown that ATP produced by oxidation of glucose was the most economic and efficient way of myocardial energy metabolism around infarcted myocardium [47]. The ATP produced by glycolysis supports the ionic pump functions [48], and the ATP produced by glucose oxidation supports the systolic and diastolic functions of myocardium [49]. The optimal metabolism and efficiency of ischemic myocardium are highly dependent on ATP produced by glucose oxidation. Several measures were taken to improve the production of ATP in myocardium, which include the addition of fructose and phosphocreatine to cold priming fluid. However, it could not significantly improve cardiac function because all of the above methods could not fundamentally solve the problem of myocardial glucose utilization. So it is important to figure out the underlying molecular mechanisms of myocardial insulin resistance to improve myocardial glucose utilization in patients undergoing CPB.

Insulin signaling involves a cascade of events, which were initiated via binding of insulin to its cell surface receptor, that subsequently autophosphorylate the receptor and activate the receptor tyrosine kinases leading to tyrosine phosphorylation of insulin receptor substrates (IRS). Phosphorylation of tyrosine residues of IRS-1 transduces signal from IR to PI3K-Akt [50,51]. Damage of insulin signaling pathway molecules leading to insulin resistance. In obesity and diabetes, decrease of insulin-stimulated tyrosine phosphorylation of insulin receptor and IRS-1 and reduced PI3-kinase activity contribute to myocardial insulin resistance [52,53]. However, compared with gradually understanding of insulin resistance in diabetics, the potential mechanism of acute myocardial insulin resistance in patients undergoing CPB is poorly understood. The mechanism of acute myocardial insulin resistance is complex and might involve a variety of pathogenic causative factors and intracellular signaling pathways. Previous studies demonstrate that the volatile anesthetic isoflurane and intramuscular telazol (tiletamine and zolazepam) and xylazine impair insulin sensitivity of skeletal muscle [54]. In this study we found that the doses given to CPB are slightly higher when compared to the sham group, but the two groups of comparative differences were not significant (not shown in this article). So the impaired insulin sensitivity of myocardial not induced by the anesthetic of propofol.

Several clinical studies provided the proof that tight glucose control by intensive insulin therapy acts as a beneficial strategy for post CPB complications [55–57], but it remains controversial for the reason of hypoglycemia and potassium metabolic disorder [4]. Insulin sensitizer, rosiglitazone, a synthetic agonist of peroxisome proliferator-activated receptor- γ has been widely used for the treatment of type 2 diabetes and insulin resistance [58], which was also reported to mitigate the myocardial insulin resistance and ameliorate the myocardial impairment

during CPB by increasing the amount of GLUT-4 expression [16]. Inactivation of Akt played a central role in CPB by inducing acute myocardial insulin resistance. SC79, a small molecule that favors the activation of Akt by specifically binding to its PH domain [59] was selected to reactivate myocardial Akt in this study. It has reported that SC79 activated Akt and protected primary murine cardiocytes from OGD/re-oxygenation in vitro [60] and H9c2 myocardial cells, but not in vivo of rat hearts [61]. In this study, we demonstrate that SC79 treatment after CPB was sufficient to activate the blunted Akt signaling, resulting in the increased myocardial membrane GLUT-4 level, augmented glucose uptake, and ATP production, which ultimately improved post CPB cardiac function. Therefore, targeting the reactivation of blunted insulin signaling, especially inactivation of Akt, may serve as a novel strategy to improve post CPB cardiac dysfunction.

In conclusion, these findings suggest that acute myocardial insulin resistance after CPB is a key detrimental factor in post CPB cardiac function, which blunts myocardial glucose uptake and ATP production via Akt inactivation. However, reactivating myocardial Akt ameliorates glucose uptake and energy supply, and ultimately favors the recovery of post operative cardiac function. These findings provided the proof that Akt inactivation induced acute myocardial insulin resistance after CPB is responsible for the post CPB cardiac dysfunction, which can also be a potential therapeutic target for the recovery of patients undergoing CPB.

Author contributions

C.H. G. contributed to the conception of the study. Z. F.W. contributed significantly to experimental design and manuscript preparation. Y.Y.W. and Q.Y. performed micro PET/CT scan. S. H. and Y.H.H. T.Z and T.C. performed echocardiography measurements and the data analyses H. M. revised and edited the manuscript.

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Competing financial interests

The authors declare no competing financial interests.

Declaration of competing interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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