Original Article

Application of Positron Emission Tomography in the Detection of Myocardial Metabolism in Pig Ventricular Fibrillation and Asphyxiation Cardiac Arrest Models after Resuscitation[*]

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Abstract

Objective   To study the application of positron emission tomography (PET) in detection of myocardial metabolism in pig ventricular fibrillation and asphyxiation cardiac arrest models after resuscitation.

Methods   Thirty-two healthy miniature pigs were randomized into a ventricular fibrillation cardiac arrest (VFCA) group (*n*=16) and an asphyxiation cardiac arrest (ACA) group (*n*=16). Cardiac arrest (CA) was induced by programmed electric stimulation or endotracheal tube clamping followed by cardiopulmonary resuscitation (CPR) and defibrillation. At four hours and 24 h after spontaneous circulation was achieved, myocardial metabolism was assessed by PET. ^{18}F-FDG myocardial uptake in PET was analyzed and the maximum standardized uptake value (SUV_{max}) was measured.

Results   Spontaneous circulation was 100% and 62.5% in VFCA group and ACA group, respectively. PET demonstrated that the myocardial metabolism injuries was more severe and widespread after ACA than after VFCA. The SUV_{max} was higher in VFCA group than in ACA group (*P*<0.01). In VFCA group, SUV_{max} at 24 h after spontaneous circulation increased to the level of baseline.

Conclusion   ACA causes more severe cardiac metabolism injuries than VFCA. Myocardial dysfunction is associated with less successful resuscitation. Myocardial stunning does occur with VFCA but not with ACA.

Key words: Ventricular fibrillation; Asphyxia; Cardiac arrest; Spontaneous circulation; Positron emission tomography; Standardized uptake value; Survival time

INTRODUCTION

The majority of cardiac arrest (CA) victims die within 72 h due to heart failure and/or ischemia-induced multi-organ failure, thus cardiopulmonary resuscitation (CPR) yields a functional survival rate of 1.4%-5%[1]. The two most prevalent causes of CA are ventricular fibrillation cardiac arrest (VFCA) and asphyxiation cardiac arrest (ACA)[2]. The two most frequently used CA animal models are VFCA and ACA[3-4]. No consent guidelines or common criteria for selection of CA models are available for experimental studies on CPR.

Myocardial stunning occurs after a brief period of myocardial ischemia despite restoration of coronary blood flow and is an important cause of post-resuscitation circulatory failure in VFCA[5]. Myocardial stunning after CPR is well known feature

of post-cardiac arrest syndrome in VFCA, but not in ACA[6]. Floating catheter, echocardiography, and gated-single photon emission computed tomography are usually used in studies of cardiac dysfunction after CPR[7]. Positron emission tomography (PET) was used in this study to characterize myocardial metabolism in VFCA and ACA animal models after resuscitation.

METHODS

Preparation of Animals

This prospective, randomized, animal study was approved by The Animal Care and Use Committee of Chaoyang Hospital and performed according to the Utstein-style guidelines[8]. Thirty-two healthy Wuzhishan miniature pigs, aged 6-8 months, weighing 20±2 kg, were randomly divided into VFCA group (*n*=16) and ACA group (*n*=16).

The animals were anesthetized by intramuscular injection of ketamine (10 mg/kg), and ear vein injection of propofol (1.0 mg/kg), followed by intravenous propofol (9 mg/kg·h) and fentanyl (1 μg/kg·h) to maintain the anesthesia level. Additional doses of these drugs were given when the heart rate exceeded 120 beats per minute (BPM) and/or systolic blood pressure exceeded 120 mmHg. The animals were mechanically ventilated with a volume-controlled ventilator (Servo 900c; Siemens, Berlin, Germany) using a tidal volume of 8 mL/kg, and a respiratory frequency of 12/min with room air. End-tidal P_{CO_2} was monitored by in-line infrared capnography (CO2SMO Plus monitor; Respironics Inc, Murrysville, PA). The respiratory frequency was adjusted to maintain the end-tidal P_{CO_2} between 35 and 40 mmHg. Aortic pressure was measured with a fluid-filled catheter advanced from the left femoral artery into the thoracic aorta. A Swan-Ganz catheter (7F; Edwards Life Sciences, Irvine, CA) was advanced from the left femoral vein into the pulmonary artery to measure the right atrial pressure and cardiac output (CO). A 5F pacing catheter was advanced from the right internal jugular vein into the right ventricle (RV) to induce VF. All catheters were calibrated before use, and their tip positions were confirmed by the presence of characteristic pressure traces. Electrocardiograph was recorded with a multichannel physiological recorder (BL-420F Data Acquisition & Analysis System). All hemodynamic parameters were monitored with a multi-function monitor (M1165; Hewlett-Packard Co, Palo Alto, CA).

Experimental Protocols

After surgery, the animals were allowed to equilibrate for 60 min to achieve a stable resting level and then baseline data were collected. VF was induced in VFCA group by programmed electrical stimuli (GY-600A; KaiFeng Huanan Instrument 90 Co, Kaifeng, Henan, China) and verified by the presence of a characteristic electrocardiographic waveform and an immediate drop in aortic blood pressure. The animals in ACA group were paralyzed with 0.2 mg/kg cisatracurium to avoid gasping and CA was induced by clamping the endotracheal tube. The animals were asphyxiated until simulated pulselessness as defined by an aortic systolic pressure <30 mmHg[3].

After CA was induced, mechanical ventilation and anesthesia/analgesia were ceased. After 8 min of untreated CA, mechanical ventilation was resumed with 100% oxygen and CPR was performed manually. Chest was compressed by a designated CPR technician. After 2 min of CPR, epinephrine (0.02 mg/kg) was injected into the right atrium followed by manual CPR for another 2 min. After 4 min of CPR, defibrillation (SMART Biphasic) was attempted using 4 J/kg on the first attempt. CPR was resumed for another 2 min after defibrillation. The sequence continued until spontaneous circulation was achieved. Spontaneous circulation was defined as the maintenance of a systolic blood pressure ≥50 mmHg for ≥10 min.

Six hours after the animals had their spontaneous circulation restored they received intensive care, mechanical ventilation was resumed with the same settings as before cardiac arrest. Six hours after resuscitation, all catheters were removed. The ventilator was switched off and the animals were ventilated by manual squeezing of the reservoir bag (F_{IO_2}=100%). Atropine (0.2 mg/kg) was given after the first spontaneous swallowing reflex appeared. The animals were extubated after adequate inspiration depth was ascertained. Vital signs were monitored throughout the recovery period. The animals were then transferred to a heated house for 18 h.

Myocardial Metabolism Imaging

To assess myocardial metabolism, ^{18}F-Fluoro DeoxyGlucose Positron Emission Tomography combined with CT (^{18}F-FDG PET/CT, GE Discovery STE, America) was performed at baseline, 4 h and 24 h after spontaneous circulation. The imaging tracer (^{18}F-FDG, 5.55 mBq/kg, >95% purity coefficient) was injected into the vein 40 min before imaging. CT

images were reconstructed with a 3.75 mm thick section at 3 mm interval. PET was performed following CT. The ^{18}F-FDG myocardial uptake was analyzed. All PET/CT images were read. A 3-dimensional region of interest (ROI; diameter 0.3 cm) was drawn on the fused PET/CT image to measure the standardized uptake value (SUV) of the whole LV: SUV=(peak kBq/mL in ROI)/(injected activity/gram body weight). Myocardial FDG uptake was expressed as the maximum SUV (SUV_{max})[9].

Statistical Analysis

The data were analyzed with SPSS 17.0 software (SPSS Inc, Chicago) and expressed as mean±SD. Continuous variables were compared between groups by a Student t-test. Differences between groups were detected by ANOVA or a paired t test or a Bonferroni t test. Survival rate was analyzed by Log Rank test. Spontaneous circulation was analyzed by Fisher's exact test where $P<0.05$ was considered statistically significant.

RESULTS

Characteristics of Animals, and Spontaneous circulation, and Survival Function

No significant difference was found in the extra doses of propofol and fentanyl administered during the preparatory phase between VFCA group and ACA group (91±12 mg vs 90±14 mg, 43±11 μg vs 41±12 μg), and in the characteristics and baseline measurements between the two groups. CA was induced in two groups (Table 1). The asphyxia time of tube clamping to CA was 12 min to 17 min.

Table 1. Parameters of VFCA Group and ACA Group After Spontaneous Circulation (mean±SD)

Items	VFCA Group (n=16)	ACA Group (n=16)	P Value
Male/Female	7/9	8/8	1.000
Body weights (Kg)	20.2±1.3	20.1±1.5	0.795
End-tidal CO_2 (mmHg)	38.2±2.4	37.9±3.1	0.883
Time of preparatory phase (min)	45.8±6.3	47.0±4.1	0.224
CA/non-CA	16/0	16/0	-
SC/non-SC	16/0	10/6	0.018

Note. VFCA: ventricular fibrillation cardiac arrest; ACA: asphyxiation cardiac arrest; CA: cardiac arrest; SC: spontaneous circulation.

Spontaneous circulation was achieved in 100% of VFCA animals and 62.5% of ACA animals ($P=0.018$). The average survival time was longer in VFCA group than in ACA group (22.50±1.10 h vs 11.16±2.66 h, $P=0.005$, Figure 1).

Comparisons of Hemodynamic Parameters

No significant difference was found in the heart rate (HR), mean arterial pressure (MAP) and cardiac output (CO) at baseline between VFCA group and ACA group ($P>0.05$, Table 2). The MAP and CO were significantly higher in VFCA group than in ACA group ($P<0.05$, Table 2), indicating that impairment of LV function is less severe in VFCA group than in ACA group.

Left Ventricular Myocardial Metabolism as Reported by Myocardial Metabolism Imaging

Myocardial metabolism imaging revealed severe radioactive sparse defects in the inferior, posterior and anterior walls of the left ventricle in both groups. However, the radioactive sparse defects were less severe in VFCA group than in ACA group (Figure 2). The SUV_{max} decreased significantly in both groups at 4 h after spontaneous circulation than baseline. The SUV_{max} was significantly higher in VFCA group than in ACA group at 4 h and 24 h after spontaneous circulation (Table 3).

DISCUSSION

In the present study, though significant myocardial metabolism dysfunction occurred in VFCA group and ACA group, ACA caused more severe cardiac dysfunction than VFCA and myocardial metabolism was associated with less successful resuscitation and
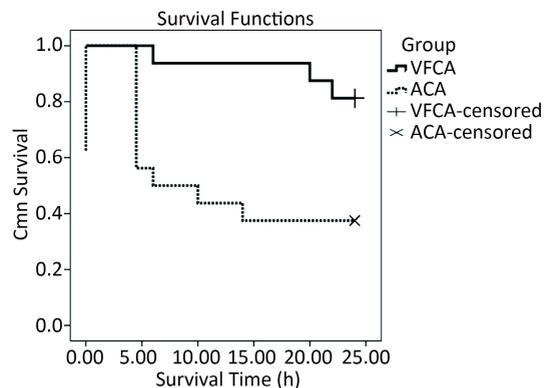

Figure 1. Survival function analysis of VFCA group and ACA group after SC.

Table 2. Cardiac Function and Hemodynamic Parameters between AFCA and ACA Groups (mean±SD)

Items	Group	Base line	1 h after SC	2 h after SC	4 h after SC	6 h after SC
HR	VFCA	101.9±7.6	112.9±8.7[*,##]	117.0±11.3[*,##]	113.7±9.5[*,##]	110.5±7.0[*,#]
(beats/min)	ACA	103.0±9.1	98.8±15.1	96.4±12.6[*]	94.5±12.7[*]	100.5±5.3
MAP	VFCA	92.9±5.5	101.4±7.9[**,#]	90.9±5.3[##]	85.0±9.0[*,##]	87.4±7.7[#]
(mmHg)	ACA	92.6±6.2	91.3±28.6[*]	77.4±23.8[*]	68.3±29.3[*]	71.0±25.1
CO	VFCA	2.9±0.2	2.2±0.2[**,#]	2.1±0.2[**,##]	1.9±0.3[**,#]	2.0±0.2[**,##]
(L/min)	ACA	3.0±0.2	1.9±0.5[**]	1.7±0.4[**]	1.6±0.3[*]	1.7±0.2[*]

Note. [*]$P<0.05$ and [**]$P<0.01$ *vs*. baseline (one-way repeated-measures ANOVA); [#]$P<0.05$ and [##]$P<0.01$ *vs*. ACA group (Student *t*-test). VFCA: ventricular fibrillation cardiac arrest; ACA: asphyxiation cardiac arrest; HR: heart rate; MAP: mean arterial pressure; CO: cardiac output; SC: spontaneous circulation.
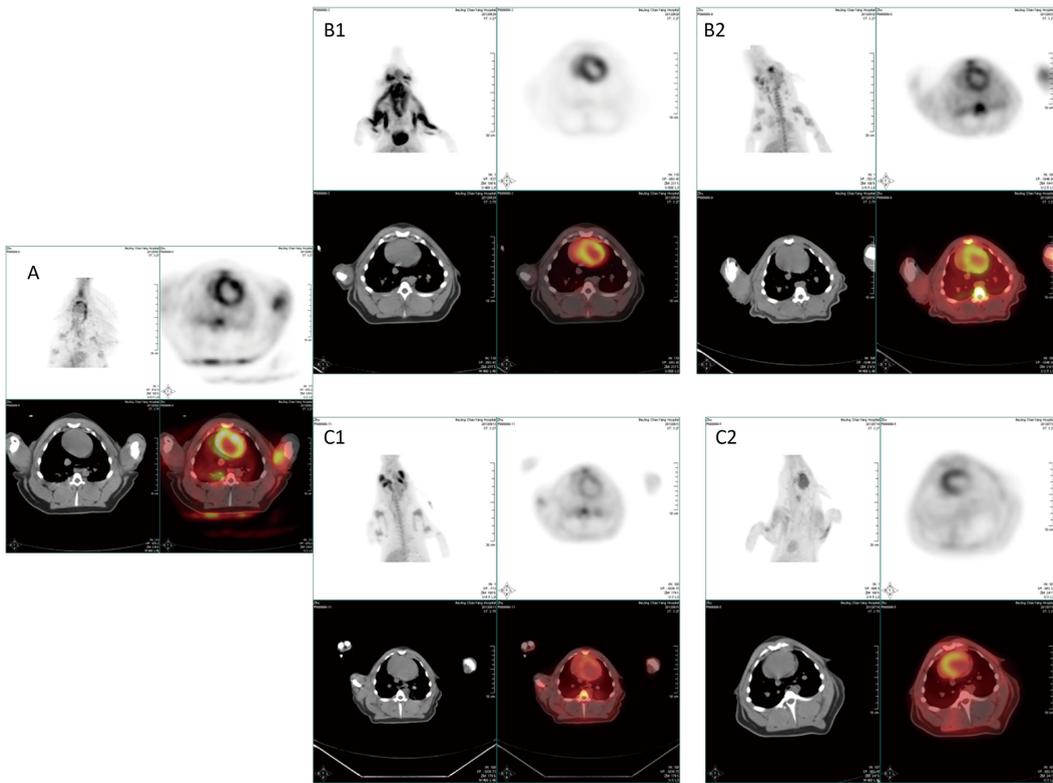

Figure 2. ^{18}F-FDG PET/CT images of myocardial metabolism in VFCA animals at baseline (A), 4 h (B1), 24 h (B2), and in ACA animals at 4 h (C1), at 24 h (C2).

Table 3. ^{18}F-FDG SUV$_{max}$ of Left Ventricle in VFCA Group and ACA Group

Groups	Base line	4 h after SC	24 h after SC
VFCA	2.56±0.15	1.95±0.13[**,##]	2.51±0.22[##]
ACA	2.55±0.20	1.00±0.17[**]	1.21±0.08[**]

Note. [**]$P<0.01$ *vs* baseline (ANOVA), [##]$P<0.01$ *vs* ACA group (Student *t*-test). VFCA: ventricular fibrillation cardiac arrest; ACA: asphyxiation cardiac arrest; CA: cardiac arrest; SC: spontaneous circulation.

shorter survival time.

It was reported that ACA results in less impairment of myocardial function than VFCA after resuscitation[2,10], which is inconsistent with our findings in this study due to the following reasons. The first was the different animal species used in previous studies[10]. The second was the different times of CA before CPR. The third was the longer asphyxiation period in this study than in previous studies. It has been shown that a period of 8 min without intervention is absolutely necessary to avoid successful resuscitation with ventilation and chest compressions alone after ACA[3,11].

In the present study, the LV function was markedly impaired following successful resuscitation in both groups whereas the MAP and CO were significantly lower in ACA group than in VFCA group, indicating that cardiac dysfunction and myocardial damage are more severe in ACA group than in VFCA group. It was reported that the LV ejection fraction in a previous study is consistent with the same conclusion in this study[12]. ACA differs from VFCA. First, the progression to complete ischemia is sudden in ventricular fibrillation and gradual in asphyxia[13]. Second, global hypoxia and hypercarbia can fully develop during asphyxia even before resuscitation, thus critically depleting the cellular energy stores. It was reported that the degree of hypoxia and ischemia is considerably greater after asphyxia than after ventricular fibrillation[14].

PET was used in this study to show what led to the distinct cardiac outcomes in the two models. Myocardial perfusion, cell membrane integrity, mitochondrial function, glucose utilization and contractile reserve can be assessed at a cardiac muscle cell level by PET[15]. ^{18}F-FDG competes with glucose for transport into the cells phosphorylated by the hexokinase reaction to ^{18}F-FDG-6-phosphate, but it is not further metabolized in cardiac muscle cells. In order to maximize myocardial uptake and overcome tracer inhomogeneity, ^{18}F-FDG is normally given after fasting[16].

PET imaging using ^{18}F-FDG is an accurate standard for assessment of myocardial hibernation and risk stratification with left ventricular dysfunction of ischemic etiology[17-18]. Dysfunctional myocardial segments with higher ^{18}F-FDG uptake represent hibernating myocardium, while reduced perfusion and metabolism suggest the presence of scars. In cases of myocardial stunning, perfusion is normal or almost normal while the ^{18}F-FDG uptake is variable[18]. Stunning refers to the phenomenon of regional contractile impairment, usually as a result of an ischemic insult, which persists for hours or weeks even after coronary blood flow restoration. It has been shown that ^{18}FDG-PET is a valuable tool for risk stratification in patients with LV dysfunction and viable myocardium by revealing worse outcomes in those not undergoing timely revascularization[19-21].

In this study, the SUV_{max} of LV was significantly lower in ACA group than in VFCA group at 4 h and 24 h after spontaneous circulation, indicating that cardiac dysfunction and myocardial damage are more severe in ACA group than in VFCA group. It was reported that myocardial stunning occurs after cardiopulmonary resuscitation in a pig cardiac arrest models of VF[22-23].

In the present study, ACA caused more severe myocardial metabolism injury than VFCA, which is consistent with the findings in a previous study[24].

Possible Limitations of the Study

Some limitations of this study should be noted, including usage of potent anesthetics, epinephrine and vasoactive agent used after spontaneous circulation, which might impair the cardiovascular function and autonomic control.

CONCLUSION

ACA causes more severe cardiac metabolism dysfunction than VFCA. Myocardial stunning occurs with VFCA but not with ACA.

ACKNOWLEDGEMENTS

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