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Original Contribution

Phosphodiesterase-5 inhibition improves macrocirculation and microcirculation during cardiopulmonary resuscitation☆

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ABSTRACT

Aim: This study is to clarify whether sildenafil, which is a selective inhibitor of the isoform 5 of the enzyme phosphodiesterase, improves macrocirculation or/and microcirculation during ventricular fibrillation (VF) and cardiopulmonary resuscitation (CPR) so as to improve outcomes of resuscitation.

Methods: Sixteen female pigs were used. After anesthesia, the abdominal cavity was opened to observe the mesenteric microcirculation. Following the guidelines, we determined microvascular flow index, perfused vessel density and proportion of perfused vessels both for large(diameter >20 μm)and small (diameter <20 μm) microvessels. Sildenafil (0.5 mg/kg) or saline was given at 30 minutes before inducing VF. After 8 min VF, 4 min CPR was started and then defibrillation was attempted.

Results: Compared with saline, sildenafil reduced the shocks and duration of CPR (all $P < .05$), and improved coronary perfusion pressure (CPP) during CPR and 24-hour survival (all $P < .05$). Sildenafil significantly improved microcirculatory parameters in large microvessel and decreased the lactic acid level during VF and CPR (all $P < .05$), but the differences in small microvessel were not significant (all $P > .05$). Microvascular flow index in both large and small microvessels were closely correlated to each other ($r = 0.91$, $P < .01$), and to CPP during CPR ([$r = .88$, $P < .01$] and [$r = .70$, $P < .05$], respectively).

Conclusion: Sildenafil increases the success of resuscitation through improving macrocirculation and microcirculation during VF and CPR. There is a close relationship between microvascular flow and CPP during CPR.

1. Introduction

As the occurrence of ventricular fibrillation (VF), which is the most common cause of cardiac arrest, macrocirculatory blood flow essentially stops. Although microcirculatory blood flow, which is the last phase of supplying oxygenated blood to tissue, also significantly reduces, flow continues for more than 3 minutes after onset of VF [1]. Microvascular blood flow is closely related to coronary perfusion pressure(CPP) which is the most important parameter of macrocirculation during cardiopulmonary resuscitation (CPR), and both are predictive of outcome [1,2]. The goal of CPR is promoting forward flow of oxygenated blood to maintain the main organs' viability until return of spontaneous circulation (ROSC) [3].

Sildenafil, which is used for treatment of erectile dysfunction and pulmonary arterial hypertension in clinic, is a selective inhibitor of the isoform 5 of the enzyme phosphodiesterase (PDE5) [4]. PDE5, which is located primarily in the cavernous body, thrombocytes, and vascular smooth muscle cells, degrades cyclic guanine monophosphate, a mediator of smooth muscle relaxation [5]. PDE5 is not present in cardiac myocytes [6], although some studies had focused on the role of PDE5 inhibition on cardioprotection effect after ischemia/reperfusion (I/R) injury [7–9]. Therefore, sildenafil may reduce I/R injury through improving blood circulation. The aim of this study is to clarify whether sildenafil increases macrocirculation or/and microcirculation during VF and CPR so as to improve results of resuscitation.

2. Methods

This study was carried out in strict accordance with the guidelines for animal care and use established by the Capital Medical University Animal Care and Use Committee. The humanistic concern for animals complies with the principles of laboratory animal use and care formulated by the Administration Office of Laboratory Animals.

2.1. Animal preparation

Sixteen female Wuzhishan pigs (30-35 kg) were used in this study. Animals were fasted overnight except for free access to water. After premedication with intramuscular injection of ketamine (20 mg/kg), anesthesia was induced by ear vein injection of propofol (1.0 mg/kg) and maintained in a surgical plane of anesthesia with intravenous infusion of sodium pentobarbital (8 mg/kg per hour). A cuffed 6.5-mm endotracheal tube was advanced into the trachea, and animals were

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mechanically ventilated with a volume-controlled ventilator (Evita4, Drager Medical, Lubeck, Germany) using a tidal volume of 15 mL/kg, a respiratory frequency of 12 breaths per minute, and F_{IO_2} at 0.21. End-tidal carbon dioxide was measured by in-line infrared capnography and maintained between 35 and 40 mmHg through adjusting respiratory frequency before induction of VF. Room temperature was adjusted to 26°C. Cardiac output (CO) was monitored with the thermodilution technique. An arterial catheter (5 F, Pulsiocath PV 2015 L20, Pulsion Medical Systems, Munich, Germany) was inserted into the descending artery through the left femoral artery for measuring arterial pressure. A 7-Fr central venous catheter was advanced from the right external jugular vein into the right atrium for measuring right atrial pressure and collection of vein blood, and used for injection of iced saline. The arterial and central venous catheters were connected to an integrated bedside monitor (PICCO; Pulsion Medical Systems, Munich, Germany) for continuous hemodynamic monitoring. A 7F sheathing canal (Edwards Life Sciences, Irvine, CA) was inserted into the left femoral vein to place an electrode catheter for induction of VF by a programmed electrical stimulation instrument (GY-600A; Kai Feng Huanan Instrument Ltd, Kaifeng, China). The abdominal cavity was opened to expose the mesentery of small intestine. Mesenteric microcirculation was visualized with the aid of a side stream dark field (SDF) imaging device (MicroScan; MicroVision Medical Inc, Amsterdam, The Netherlands).

Sildenafil was obtained from a 25-mg Viagra (Pfizer, West Ryde, Australia) tablet that was dissolved in 50 mL saline, filtered and stored at 4°C.

2.2. Microcirculatory imaging

Mesenteric microcirculation imagings were recorded by an SDF imaging video microscope with a 5× optical probe. A hand-held video microscope emits stroboscopic green light, which is absorbed by hemoglobin. The negative image of moving red blood cells is transmitted back to a camera. The SDF image shows a region of interest of approximately 1000 × 750 μm. Individual videos of 10 seconds were analyzed offline using a score previously described by Spronk et al [10], in which 0 represents no flow, 1 represents markedly reduced flow, 2 represents reduced flow, and 3 represents normal flow.

2.3. Experimental procedures

After surgery, the animals were allowed to equilibrate for 30 minutes to achieve stable resting level and, then, were given sildenafil (0.5 mg/kg) or saline by vein injection. The investigators were blinded to the drug treatment. Half an hour after administration, VF was induced by programed electrical stimulation, mode S1S2 (300/200 milliseconds), 40v, 8:1 proportion, and −10-millisecond step length [11]. VF was verified by electrocardiogram and blood pressure. After successful inducing of VF, mechanical ventilation was discontinued and electrode catheter was extracted. CPR was started after 8 minutes of untreated VF. Manual chest compressions were immediately initiated at a rate of 100 compressions per minute. Ventilation was performed by bag respirator with room air, and compression-to-ventilation ratio was 30:2. The quality of chest compressions was controlled by a Heart Start MRx Monitor/Defibrillator with Q-CPR (Philips Medical Systems, Best, Holland). Defibrillation was attempted after 4-minute CPR. Defibrillation shock was administered at 120 J (Smart Biphasic) for the first attempt. All subsequent attempts used the 150-J dose. If the first defibrillation was unsuccessful as indicated by arterial pressure and electrocardiogram monitoring for 5 seconds, another 2-minute CPR continued. Mechanical ventilation with 100% oxygen was started at the beginning of the first defibrillation attempt and continued until ROSC, after which room air was used. ROSC was defined as maintenance of systolic blood pressure at least 50 mmHg for a continuous period of at least 10 minutes. Animals were announced dead if 4 times of defibrillation were attempted but there was still no ROSC. After ROSC, animals underwent a 4-hour intensive care period with administration of Ringer solution (20 mL/kg), and then all vascular catheters were removed. The abdominal cavity was closed after ROSC. Animals were allowed to recover from anesthesia, placed in observation cages, and monitored every 2 hours until 24 hours after resuscitation. Water was given during the observation period. Tramadol hydrochloride (50 mg) was given by intramuscular injection every 12 hours to ease the pain. The experimental procedure is shown in Fig. 1.

2.4. Measurements

Hemodynamic data (CO, mean arterial pressure [MAP], and right atrial pressure [RAP]) were continuously measured and recorded. CPP was measured from the differences in time-coincident diastolic aortic and right atrial pressures during diastole. During CPR, CPP was measured during the relaxation time of chest compression. Microcirculatory images were obtained at baseline; 30 minutes after infusing sildenafil; 1, 4, and 7 minutes after onset of VF; and 1 and 3 min after start of CPR. Mixed venous blood samples for lactic acid level analyses were drawn at the same time. Following the guidelines [10], we determined microvascular flow index (MFI), perfused vessel density (PVD), and proportion of perfused vessels (PPV) both for large microvessel (diameter >20 μm) and small microvessel (diameter <20 μm). Two technical personnel performed the analysis independently, and their results were averaged.

2.5. Statistical analysis

Results are expressed as mean ± SD. Discrete variables, such as ROSC and 24-hour survival, were compared with Fisher exact test. Continuous variables were compared by repeated measures and multivariate analysis of variance or using the Student *t* test, as appropriate. Linear correlations were calculated using the Pearson correlation coefficient. $P < .05$ was regarded as being statistically significant. All analyses were conducted using the SPSS 17.0 software (SPSS Inc, Chicago, IL) and GraphPad PRISM version 5 (GraphPad Software Inc, San Diego, CA).

3. Results

ROSC was achieved in 7 of 8 pigs in the sildenafil group and in 5 of 8 pigs in the saline group ($P > .05$). There were seven pigs survived for more than 24 hours in the sildenafil group, but only 3 pigs in the saline group ($P < .05$). The shocks of survivor and duration of CPR before ROSC in the sildenafil group were less than those in the saline group (all $P < .05$) (Table. 1).

Compared with baseline, the MAP, RAP, CPP, and CO values decreased significantly in the sildenafil group at 30 minutes after infusion (all $P < .05$). As the occurrence of VF, the MAP, CPP, and CO values suddenly decreased, but RAP increased in both groups. The RAP values were lower in the sildenafil group than in the saline group at 1, 4, and 7 minutes of VF and at 1 and 3 minutes of CPR (all $P < .05$). Although the MAP values were also lower in the sildenafil group than in the saline group during VF and CPR, the differences were not significant (all $P > .05$). The CPP and CO values dropped to near zero and could not be measured during VF. During CPR, there were no significant differences in the CO values between the 2 groups (all $P > .05$), but the CPP values were higher in the sildenafil group than saline group(all $P < .05$) (Fig. 2).

In both groups, mesenteric microvascular blood flows were dramatically reduced within the 1-minute period as the occurrence of VF, followed by a continuous decrease. Microcirculatory blood flow was improved with the start of CPR (videos 1, 2, and 3, respectively, on behalf of microcirculation image at baseline, VF 4 minutes, and CPR 4 minutes in the saline group; videos 4, 5, and 6, respectively, on behalf of microcirculation image at baseline, VF 4 minutes, and CPR 4 minutes in the sildenafil group).

Compared with saline, sildenafil significantly improved microcirculatory parameters (PVD, PPV, and MFI) in large microvessel during VF