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A Rat Model of Cardiopulmonary Bypass with Excellent Survival

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Background. **Elucidating the underlying mechanisms and developing protective strategies for the pathophysiological consequences of cardiopulmonary bypass (CPB) have been hampered due to the absence of a satisfactory long-term recovery animal model. The objective of this study was to establish a survival experimental model of CPB in rats to meet the requirement of these studies.**

Materials and methods. **Male SD rats (450–550 g) were randomly divided into CPB (n = 10) group and Sham group (n = 10). All rats were anaesthetized and mechanically ventilated. The femoral artery and vein were cannulated for continuous blood pressure recordings and fluid replacement, respectively. The CPB circuit comprised a venous reservoir, a membrane oxygenator, and a roller pump. Blood was drained from the right atrium via a jugular vein catheter and returned to the right carotid artery. Priming consisted of 8 ml of homologous blood and 8 ml of colloid. CPB was conducted for 60 min at a flow rate of 100–150 ml/kg/min in the CPB group. Haemodynamic investigations, blood gas analysis, and survival studies were performed subsequently.**

Results. **Our data show that the rat model principally simulated the clinical setting of CPB in terms of its construction, configuration, performance, material surface area, and priming volume to blood volume ratio. All CPB rats survived and the 2-week follow-up period remained uneventful.**

Conclusions. **The rat model of CPB was easy to establish and was associated with excellent survival. This model should facilitate the investigation of the pathophysiological processes concerning CPB-related multiple organ dysfunction and possible protective interventions.** **© 2004 Elsevier Inc. All rights reserved.**

Key Words: **rats; animals; disease models; cardiopulmonary bypass; heart surgery; experiment; systemic inflammatory response; pathophysiology.**

INTRODUCTION

Cardiopulmonary bypass (CPB) is an essential component of conventional cardiac surgery and may be used in many other surgical procedures [1]. Despite excellent improvements, the manifestations of postperfusion syndromes such as clinical signs of pulmonary and renal dysfunction, neurological and gastrointestinal injury, coagulation disorders, and hemolysis, increase in interstitial fluid, and susceptibility to infections have been repeatedly reported [2–5]. The underlying mechanisms are probably multifactorial, including surgical trauma, anaesthetic effects and muscle paralysis, increase in capillary permeability, and impacts of the CPB apparatus [5, 6]. In order to clarify the pathophysiological processes, numerous experimental studies have been developed [7–10], but most have been performed in larger animal models, such as dogs, sheep, pigs, rabbits, etc. These models have substantial limitations because they are extremely expensive, they utilize very complex instruments, and are labor intensive.

The rodent model of CPB can reduce the cost of animals and equipments, and there are a large availability of assays. Previous attempts at developing rat CPB models have been successful to some extent [11–19], but most of them were partial bypass or depended on large quantities of priming. Few studies referred to a truly clinically relevant model of complete CPB dealing with the fluid flow, surface area, and priming volume of the circuitry in the literature. Our aim was to develop a rat CPB model with consistent survival for a related

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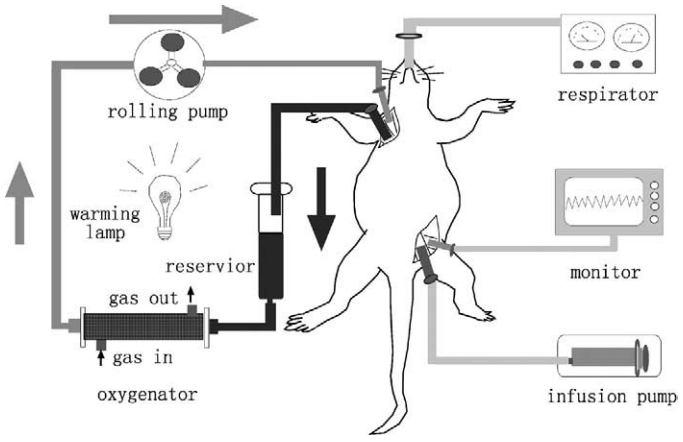

FIG. 1. Schematic diagram of surgical procedure and rat CPB apparatus.

long-term (>72 h). With this technique, we were able to study the CPB-related multiple organ dysfunction in detail by characterizing the mechanical and histological changes and to further search the therapeutical strategies.

MATERIALS AND METHODS

Animal Preparation

Adult male Sprague-Dawley rats (450–550 g) were used for all experiments. The animals were obtained from the Chinese Academy of Science, Nanjing University Animal Centre. All animals received humane care in compliance with "The Principles of Laboratory Animal Care" formulated by the National Society of Medical Research and "The Guide for the Care and Use of Laboratory Animals" published by the U.S. National Institutes of Health (Publication No. 85–23, revised 1996). The following experimental protocol was approved by the Nanjing University Animal Care and Use Committee. The rats were housed and fed at the Animal Center of Jinling Hospital for at least 7 days before surgery to allow them to adjust to the environment.

Surgical Procedure

Rats were anaesthetized with intraperitoneal administration of ketamine (50 mg/kg) and chlorpromazine (2 mg/kg). In order to reduce respiratory secretion, atropine (0.1 mg/kg) was also added to the agents. Once surgical-level anaethesia was achieved, the rats were secured supine. A polyethylene cannula (internal diameter 3 mm) was inserted into the trachea and the lungs were mechanically ventilated with a small animal ventilator (Rodent Respirator, TKR-200C, China). The tidal volume was approximately 10 ml/kg, the respiratory rate was 60 breaths/min, and the respiration concentration of O_2 was 100%. Ventilation was finely adjusted to keep an arterial carbon dioxide tension ($PaCO_2$) of 35–45 mmHg. Anaesthesia was maintained throughout the experiment with additional doses of intravenous ketamine. All subsequent procedures were performed under aseptic conditions.

The right femoral artery was cannulated with a 24-gauge Teflon heparinized catheter to monitor systemic arterial pressure (SAP) and to collect arterial blood for arterial blood gas analysis (blood gas analyzer, GEM Premier 3000, USA). The homolateral femoral vein was cannulated with a 20-gauge catheter for blood and fluid replacement. Following administration of heparin (500 U/kg), a 16-gauge catheter, modified to a multiside-orifices cannula in the forepart, was inserted into the right jugular vein and advanced to the right atrium. This position resulted in excellent drainage which could support high flow (>100 ml/kg/min) perfusion for complete CPB. A 22-gauge catheter was cannulated to the right carotid artery which served as the arterial infusion line for the CPB circuit.

Perfusion Circuit

The minute CPB circuit comprised a venous reservoir, a specially designed membrane oxygenator, a roller pump, and sterile tubing with an inner diameter of 4 mm for the venous line and of 1.6 mm for the arterial line. The blood was drained from the right atrium via a jugular vein catheter to a 10 ml sterile open reservoir by gravity and siphon. The relatively large venous tube (4 mm) and the high siphon level (30 cm) overcame the resistance of drain flow and induced to a satisfaction venous return. The membrane oxygenator was specially designed with a surface area for gas exchange of 0.05 m^2 (Micro-1, Kewei Medical Instrument Inc., China) and was made of the fibre commonly used in clinical devices. The total assembly dynamic priming volume approximated 4 ml. A rolling pump (BT00-300M, Lange Co., China) was used to drive the blood through silicone arterial inflow tubing (1.6 mm) and then to return to the right carotid artery. Body central temperature was monitored with a rectal probe and kept at 36.5–38.3°C by a heat lamp placed above the animal and the CPB equipment.

Priming was composed of 8 ml heparinized homologous blood obtained from a donor rat immediately before the experiments and 8 ml synthetic colloid (HAES-steril). During the experiments, to ensure the mean arterial pressure above 60 mmHg and the hematocrit about 30–40%, additional whole blood and Ringer's solution might be given in order to replace the blood and fluid loss caused by operation, sampling, leakage, and evaporation. With an inspired oxygen fraction of 100%, 50 ml/min gas flow was sufficient to achieve adequate oxygenation and to maintain the $PaCO_2$ within 35–45 mmHg. At the initiation of perfusion, the flow-rate was gradually adjusted to a level that would sustain the arterial pressure near 80 mmHg. At this point, mechanical ventilation was terminated and CPB was stable performed at 100–150 ml/kg/min throughout the experiment. After 60 min, the bypass was terminated and the cardiac function was retained with heart beating and pulsation. The remaining priming solution was infused gradually when the main arterial pressure was less than 60 mmHg (see Figs. 1 and 2).

Experimental Protocol

Rats were randomly submitted to both the CPB and the Sham groups and both included 10 rats. The experimental preparation,

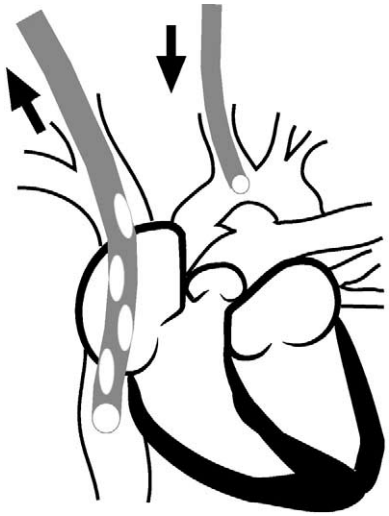

FIG. 2. Schematic diagram of vascular canulation technique in cardiac system.

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