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Deleterious effects of aggressive rapid crystalloid resuscitation on treatment of hyperinflammatory response and lung injury induced by hemorrhage in aging rats

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ABSTRACT

Background: Large-volume, rapid crystalloid infusion may increase endothelial cell damage and induce shear stress, potentially leading to multiple-organ dysfunction syndrome. Limited guideline data for fluid administration are currently available, especially for the aging population. The aim of the present study was to compare the degree of organ damage in conscious aging rats when different resuscitation speeds were used during the treatment of hemorrhagic shock (HS).

Methods: Eighteen aging male Wistar-Kyoto rats were randomly divided into the following three groups: the control group, 30-min rapid resuscitation group, and 12-h slow resuscitation group. To mimic HS, 40% of the total blood volume was withdrawn. Fluid resuscitation (1:3) was given at 30 min after the blood withdrawal. Blood biochemical parameters including glucose, lactic acid, and lactate dehydrogenase (LDH) were measured along with the levels of serum and bronchoalveolar lavage fluid, tumor necrosis factor alpha (TNF-α), and interleukin 10 by enzyme-linked immunosorbent assay. The lungs were examined for pathologic changes, and the injury score at 24 h after HS was calculated.

Results: Compared with slow-rate resuscitation, initially rapid and immediate resuscitation significantly increased the serum levels of glucose, LDH, and proinflammatory cytokines (TNF-α and interleukin 10), and bronchoalveolar lavage fluid levels of white blood cells, TNF-α, and LDH as well as produced pathologic changes in the organ. The lung injury scores were higher after induced HS in aging rats.

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Conclusions: The slow and continuous (12 h) fluid resuscitation rate ameliorated HS-induced organ damage in conscious aging rats.

1. Introduction

Fluid resuscitation is a common treatment modality for many kinds of circulatory shock, especially for traumatic hemorrhagic shock (HS) [1]. An initial and large-volume crystalloid resuscitation is frequently recommended for acutely bleeding patients [2]. However, several recent experimental and clinical studies have questioned the initial therapeutic goal of normalizing blood pressure with large-volume isotonic crystalloid solutions [3], because this approach increases endothelial cell damage, induces shear stress, and can lead to multiple-organ dysfunction syndrome [4]. On the other hand, slow and limited fluid resuscitation has been beneficial in multiple HS animal studies because it prevents increased bleeding during HS, induces mild hypothermia, and suppresses the release of systemic proinflammatory cytokines (tumor necrosis factor alpha [TNF-α] and interleukin 6 [IL-6]) and the expression of TNF-α and nitric oxide in the lungs after HS [5].

Evidence from clinical observation and experimental animal models reveals that aging is associated with an increased proinflammatory state, and the results of the present study are similar to those seen in the two-hit model of injury [6]. In the initial proinflammatory phase, the release of proinflammatory mediators such as TNF-α, IL-6, IL-8, and the platelet-activating factor into circulation increased, putting the elderly patient at a significant risk for early multiple organ failure because of inflammatory-mediated destruction of vital organs such as heart and lungs, as well as shock, in which hypoperfusion renders tissues incapable of sustaining aerobic metabolism [7]. Moreover, age-related changes in the respiratory systems include pulmonary hyperinflation, a decrease in pulmonary elasticity, and a decline in the immune system with changes in phagocyte function. Dysregulation of the Kupffer cells in liver with aging may alter the inflammatory response that decreases the function of phagocytosis, endocytosis, immunomodulation, and synthesis and secretion of numerous proinflammatory and anti-inflammatory mediators [6].

Slow-rate resuscitation induced mild hypothermia and suppressed the release of proinflammatory cytokines (TNF-α and IL-6) after HS, decreasing the organ injury associated with HS in young rats [5]. In contrast, we found little evidence in the research regarding optimal fluid resuscitation of elderly patients or animals in traumatic situations. Therefore, we hypothesized that low-rate and limited-volume fluid resuscitation in the early stage may induce hypoinflammatory response to ameliorate HS-induced organ damage in aging rats. This study explores the pathogenesis of HS and fluid resuscitation in an aging rat model. We investigated the effects of different speeds of large-volume resuscitation on inflammatory cytokines and organ damage after HS.

2. Materials and methods

2.1. Experimental model

The University Committee for Animal Use and Care has approved this study. Eighteen aging male Wistar-Kyoto rats, 18-mo old, weighing 420–460 g, were purchased from the National Laboratory Animal Center (Taipei, Taiwan) and housed in the University Animal Center at 22 ± 1°C, with the humidity at 60 ± 5% and a 12-h light–dark cycle. Food and water were provided *ad libitum*. The animals were anaesthetized by ether inhalation before the experiment and catheters (polyethylene 50 [PE-50], Clay Adams, Parsippany, NJ) were separately inserted into (1) the right femoral artery for connection to a pressure transducer (Gould Instruments, Cleveland, OH) to record the arterial pressure (Power Laboratory, AD Instruments, Mountain View, CA) and (2) the right femoral vein for blood withdrawal using an aseptic surgical technique [5,8]. The surgical procedure was completed within 15 min leaving a wound less than 0.5 cm^2.

Each animal was placed on an individual metabolic plate overnight after the procedure. The rats' tails were tied securely to prevent them from running randomly on the plate. During the experiment, the physiological changes and body temperature were continuously monitored every minute using a digital thermometer (HR 1300 thermometer; Yokogawa, Tokyo, Japan); the rats were in a conscious state for 24 h. The thermocouple probes of the thermometer were inserted approximately 5 cm into the rectum to monitor the core temperature, and the outside wire was affixed to the tail using tape.

2.2. HS model

Arterial blood samples were used as baseline values before the blood withdrawal, which was conducted as described previously [9]. HS was induced by drawing blood from the femoral arterial catheter into a 10-mL syringe. An infusion pump controlled the withdrawal rate to mimic a typical bleeding event. The volume of blood withdrawn was 40% of the total blood volume to produce a grade III hemorrhage [5,10], which was calculated as 6 mL × (gram body weight/100) [11]. The duration of the blood withdrawal was 30 min; the animals were further observed for 24 h and then euthanized for later pathologic analyses.

2.3. Fluid resuscitation

The rats were assigned to the control, rapid resuscitation, or slow resuscitation groups. Fluid resuscitation was started at 10 min after the blood withdrawal. Crystalloid-normal saline (NS) was given at a ratio of 1:3 against the expected blood