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Circulating Blood Volume in Burn Resuscitation

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ABSTRACT

Circulating blood volume (CBV) was prospectively measured in patients with almost solely smoke inhalation injury (Group I: 10 patients) and in patients with severe cutaneous burn (Group B: 6 patients) consecutively until 96 hours after injury, to assess the effect of either injury on intravascular volume status by the pulse dye-densitometry method. All participants were treated by an ordinary fluid regimen based on the Parkland formula with an hourly urine output of 1.0 to 2.0 ml/kg for the resuscitation endpoint. CBV was also measured in 15 elective surgical patients for a control value (76.7 ± 9.0 ml/kg). The level of CBV values in Group I was low, ranging from 54.4 ± 6.9 ml/kg to 59.6 ± 6.2 ml/kg (from 70.9% to 77.7% of control value), while in Group B from 48.5 ± 5.5 ml/kg to 55.6 ± 17.3 ml/kg (from 63.2% to 72.5%) until 72 hours after injury. There was no significant difference in CBV values between the two groups throughout the study period.

We could elucidate the existence and extent of intravascular volume depletion in spite of optimal fluid treatment in both solely smoke inhalation injury and solely severe cutaneous burn. Almost solely inhalation injury was found to decrease CBV to less than that of severe cutaneous burn, which presumably led to the increased fluid requirement. Concerning the resuscitation endpoint in early burn treatment, this depletion in CBV must be taken in mind. Hourly urine output is speculated to be an effective and practical clue to manage a burn patient within permissive hypovolemia.

Key words: *Smoke inhalation injury, Burn resuscitation, Circulating blood volume, Pulse dye-densitometry*

Fluid replacement in burn patients in recent experience has been guided by volume restoration formulas derived from clinical observation and experimental data. The most commonly used formula is the Parkland formula, which calls for the patient to receive 4 ml of lactated Ringer's solution per kilogram body weight per percent of burn during the first 24 hours after injury[5,35]. It is recognized that the formula is only a guide and that an adjustment of fluid infusion rate is required usually based on the clinical responses of blood pressure, heart rate and urine output in the patient. The overall resuscitation goal recommended in the formula is to control urine output in the range of 0.5 to 1.0 ml/kg/hr for adult patients to prevent "overresuscitation" which results in acute pulmonary edema.

Conversely, Dries and Waxman have documented that urine output, blood pressure and heart rate provide inaccurate and insensitive information concerning the adequacy of burn resuscitation[11]. This is of particular concern because the use of these traditional circulatory resuscitation endpoints might increase the likelihood of "unrecognized underresuscitation"[31]. At the same time, smoke inhalation injury itself has been known to produce systemic pathologic changes as manifested by increased fluid requirements and a significantly greater mortality[6,15,29,33]. However, the resuscitation status in smoke inhalation injury has not been adequately studied.

The recently developed technique of pulse dye-densitometry has enabled convenient measurement of circulating blood volume of the patients at bedside. In order to elucidate the extent of hypovolemic status in burns and in inhalation injury patients, a prospective study of circulating blood volume (CBV) level was conducted.

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PATIENTS AND METHODS

The study and procedure were approved by the Ethical Committee of Hiroshima University Medical Hospital and written informed consent was obtained from the selected patients or from their families. To determine the magnitude of the effect of smoke inhalation injury or of cutaneous burn injury on circulating blood volume, two characteristic groups were composed as follows:

Group I: patients with solely smoke inhalation injury.

Group B: patients with solely cutaneous burn injury.

As a patient suffering from inhalation injury is not always free from cutaneous burn, patients with less than 20% of TBSA burned within which non-burn tissue edema was not likely to develop were permitted to enter Group I. Patients with larger than 25% of TBSA burned with no inhalation injury were accepted to enter Group B. Other criteria for admission to the study were: patients over 15 years of age who were admitted to our institute within 2 hours after injury and whose fluid intake and output were precisely measured without concomitant complications or illness that affected his/her urine output or fluid demand and not resigned resuscitation. The depth and extent of burn were assessed and recorded according to Lund and Browder's diagram[9]. Diagnosis of smoke inhalation injury was established by physical examination and bronchoscopic findings[27]. Group I consisted of 10 patients and Group B of 6 patients.

Treatment was conducted by the ICU staff and dermatologists. The initial fluid requirement was estimated according to the Parkland formula, and the rate of fluid administration was modified flexibly according to the clinical response of blood pressure, heart rate and urine output of the patient: an hourly urine output of 1.0 to 2.0 ml/kg was used as the principal resuscitation endpoint. Patients in Group I were given maintenance fluid in proportion to physique and lactated Ringer's solution was additionally administered to meet the resuscitation endpoint. Patients in Group B were given lactated Ringer's solution in accordance with estimation of the Parkland formula with flexible modification to meet the same endpoint. Colloid solutions were administered at 8 hours after injury when indicated. Dopamine was administered to all patients in a dose ranging from 2 to 5 μg/kg/min to support hemodynamic performance.

Direct arterial pressure monitoring was conducted in all patients. A central venous catheter was placed in the subclavian, internal jugular vein or femoral vein for administration of fluids and inotropes and for central venous pressure (CVP) monitoring. Other invasive monitoring devices such as thermodilution catheters were not applied. A mechanical ventilatory support with intubation was indicated if the existence of smoke inhalation injury was suspected and the burn size exceeded 60%, and prophylactic intubation was often indicated if the development of airway and cardiopulmonary complications was suspected. All participants in Group I were intubated and managed with mechanical ventilation, as were 5 of 6 patients in Group B.

Escharotomy was performed on admission if dangerous thoracic constriction or malperfusion in peripherals was observed. Wounds were treated with topical antimicrobial creams and cleansed daily by the dermatological team. Surgical excision of necrotic burned tissue and autografting were not performed in any patient during the study period.

Age, gender, physical status such as height, weight and body surface area of the patients was recorded. The burn size and depth were extracted from the diagram, and the burn index (half of second degree burn + third degree burn) and prognostic burn index (burn index + age) were calculated to demonstrate the severity of cutaneous burn. Elapsed time to commencement of treatment after injury was extracted from medical records and compared. The following clinical parameters were also recorded: mean arterial blood pressure, heart rate, body temperature, CVP, urine specific gravity, PaO_2/FiO_2 ratio, hematocrit, white blood cell count, serum C-reactive protein level and serum lactate level. The values of these parameters were obtained consecutively at 8, 16, 24, 48, 72 and 96 hours after injury. Serum C-reactive protein and urine specific gravity were measured daily until day 4 and the values of serum C-reactive protein were also determined at day 7.

Circulating blood volume (CBV) was measured at the same time interval as the other parameters according to the pulse dye-densitometry method (DDG analyzer-2001, Nihon Kohden, Tokyo, Japan), using indocyanine green (ICG) as dye13,18). To minimize systematic error and measurement error, the measurement procedure was established in a written form before commencing the study. We uniformly used 20 mg of ICG (Diagnogreen, Daiichi Pharmaceutical, Tokyo, Japan) diluted with 5 ml of distilled water in each measurement. Dye was injected via a central venous catheter at bolus followed by a flush of 20 ml of saline to wash out the line. A three-way cock nearest to the patient was used for injection to minimize residual dye in the line. Patients were not always in the supine position; a tilt within 5 degrees and slightly lateral inclination were accepted. Measurements were performed while patients were in a stable state. Measurements during aggressive infusion, soon after changing the administration rate of dopamine, during or soon after tracheal suction, or while patients were in aggressive motion were avoided. As the detec-

tion probes used were essentially the same as those utilized in the pulse oximetry method, motion of the patient can lead to movement of the probe or motion artifact and thus to a false value. The location of the probe was chosen to detect the finest arterial pulsation. Fingers were sometimes not available because of burn and wrapping; nostril, earlobe or lips were also used for measurement. The following information was required for precise measurement: amount of injected ICG (20 mg here), hemoglobin level, and the height and weight of the patient. The hemoglobin level was measured at each measurement (Celltac α, Nihon Kohden, Tokyo, Japan). Results were all printed with a dye-densitogram and then thoroughly examined. CBV was also measured in 15 elective surgical patients in the operating room just after induction of anesthesia and before incision, and the mean value and standard deviation calculated were employed as the control value of CBV.

Statistical analysis

Differences in the values of age, gender ratio, height, weight and body surface area among the three groups comprising Group I, Group B, and the 15 surgical patients from which the control CBV value was obtained were analyzed by one-way analysis of variance and the Kruskal-Wallis test. Differences in non-parametrical values such as %TBSA burned, burn index, prognostic burn index and elapsed time to treatment between the two groups of Group I and Group B were analyzed by Mann-Whitney U-tests, and physiological parameters between the two groups were analyzed by Student's unpaired t-tests. The significance of difference in mortality was tested by a Chi-square test. Analysis of variance with Fisher's protected least significant difference was applied for consecutively measured values and for comparison among the three values of CBV including control. Statistical significance was defined as $p < 0.05$. All values in the table and figures are given as means ± standard deviation. The range and median of chief non-parametrical values such as age, %TBSA burned and elapsed time to admission are also given in the table.

RESULTS

The demographics and clinical characteristics of the patients are presented in Table 1. There were no significant differences in age, gender and physical status among the three groups including control. There were significant differences between the two groups in severity of burns as Group I was defined as minor burn and Group B as extensive burn.

The amount of fluid administered and urine output at 24-hour intervals until 96 hours after injury are presented in Fig. 1. Within the initial 24 hours, a significantly greater amount of fluid was administered compared to the later periods in both groups. The amount of fluid administered was significantly greater in Group B than in Group I except from 24 to 48 hours. Urine output was controlled within 1.0 to 2.0 ml/kg/hr and no difference was observed between the two groups throughout the study period.

The time course of all physiological parameters is shown in Fig. 2. No significant differences in vital signs such as mean arterial blood pressure, heart rate, body temperature, CVP and urine specific gravity between Group I and Group B were observed throughout the study period except heart rate at 72 hours. No significant difference in respiratory impairment was detected with PaO_2/FiO_2 ratio throughout the study period. There was no difference in hematocrit in the first 72 hours. The values of serum C-reactive protein did not differ

Table 1. Demographics and clinical characteristics of the patients

	control	Group IB	Group B	P values
Number of patients	15	10	6	
Age mean ± SD	61.9 ± 11.0	53.4 ± 26.19	72.5 ± 12.3	
range (median)	32–82 (63.0)	15–88 (50.5)	49–82 (75.5)	n.s.
Gender (male/female)	10/5	5/5	2/4	
Physical status				
Height (cm)	160.2 ± 6.7	159.0 ± 8.5	154.2 ± 8.0	n.s.
Weight (kg)	54.6 ± 5.7	56.9 ± 12.7	51.5 ± 7.4	n.s.
Body surface area (m^2)	1.57 ± 0.09	1.61 ± 0.15	1.48 ± 0.14	n.s.
Severity of burn				
%TBSA burned (%) mean ± SD	—	8.9 ± 7.6	45.8 ± 17.1	
range (median)	—	0–19.9 (6.3)	26.–68.0 (40.5)	< 0.0001
Burn index*	—	5.2 ± 5.5	29.0 ± 13.8	0.0002
Prognostic burn index†	—	58.6 ± 29.8	101.6 ± 12.4	0.0050
Time to admission (min) mean ± SD	—	40.9 ± 15.2	57.0 ± 31.3	
range (median)	—	19–70 (40)	30–102 (45)	n.s.
Deaths	—	0	2	n.s.

* Burn index = second degree burn (%) × 1/2 + third degree burn (%)

† Prognostic burn index = burn index +age

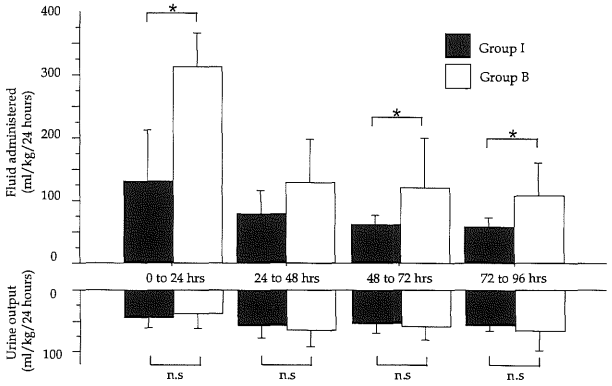

Fig. 1. Comparison of amount of fluid administered and urinary output between Group I and Group B. Urinary output is depicted downward. The solid bar and open bar represent mean ± SD of values of Group I and Group B, respectively. Asterisk indicates a statistically significant difference between the groups.

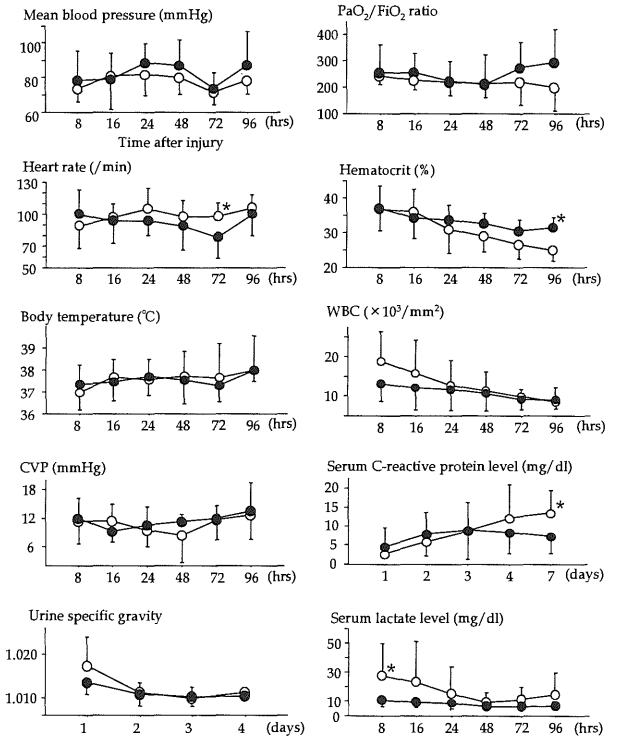

Fig. 2. Comparison of each parameter between the two groups. The solid circles and open circles represent the values of Group I and Group B, respectively. Asterisk indicates a significant difference between the two groups.

significantly until day 7. The serum lactate level in Group B was significantly higher than that in Group I at 8 hours after injury, but gradually decreased to reach normal range within 48 hours. In Group I, serum lactated values were maintained around normal range.

The control value of CBV obtained from surgical patients was 76.7 ± 9.0 ml/kg. The time course of CBV values in Group I and Group B is shown in

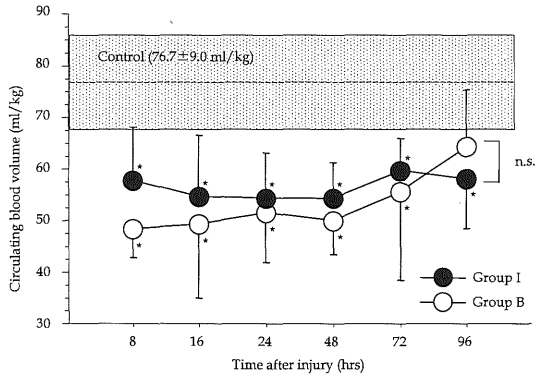

Fig. 3. Comparison of circulating blood volume between Group I and Group B. The dotted square represents mean and SD of the control value. The solid and open circles represent values of Group I and Group B, respectively. Asterisk indicates a significant difference between control level and values of each group. Circulating blood volume in both groups was significantly lower than control level except that of Group B at 96 hours after injury. There was no significant difference between Group I and Group B throughout the study period.

Fig. 3. The CBV value in Group I was significantly lower at 8 hours after injury: 57.7 ± 10.3 ml/kg (75.2% of the control value: p = 0.0001). The value gradually decreased to reach the minimum level at 48 hours: 54.4 ± 6.9 ml/kg (70.9%: p <0.0001). The value slightly increased thereafter, but did not reach the control value until 96 hours: 59.6 ± 6.2 ml/kg at 72 hours (77.7%: p = 0.0004). The CBV value in Group B was also significantly lower in level at 8 hours after injury: 48.5 ± 5.5 ml/kg (63.2% of the control value: p < 0.0001). The values gradually but slightly increased thereafter, marking 51.5 ± 9.7 ml/kg at 24 hours, 49.9 ± 6.4 ml/kg at 48 hours and 55.6 ± 17.3 ml/kg at 72 hours (67.1%, 65.1% and 72.5% of the control value, respectively: all p values were below 0.002). CBV values in Group B reached 64.4 ± 11.6 ml/kg at 96 hours after injury, when statistical significance was not detected compared to the control level: 84.0%, p = 0.0551. There were no statistically significant differences detected between the CBV values of Group I and those of Group B throughout the study period.

DISCUSSION

Fluid resuscitation has been required to prevent intravascular volume depletion without causing overhydration and the subsequent development of pulmonary edema or excessive peripheral edema. We have applied an hourly urine output of 1.0 to 2.0 ml/kg/hr as a principal resuscitation endpoint which is slightly greater than that recommended in the traditional formula. We have never experienced a resuscitation failure that resulted in acute renal failure or liver failure with this guideline for more than ten years, and the incidence of pul-

monary edema was similar to that of other reports[20,32,33].

Conventional clinical parameters such as blood pressure, heart rate, body temperature, CVP and hematocrit are commonly regarded as reflecting the presence and the extent of hypovolemic status[9]. These parameters demonstrated similar changes after smoke inhalation and cutaneous burn injury. The larger serum lactate level in cutaneous burn may promote an intuitive understanding that the extent of hypovolemia is much greater in severe cutaneous burn and thus less attention is given to the treatment of smoke inhalation injury.

The most striking result was the existence and similar extent of hypovolemia in both clinical situations of almost solely smoke inhalation injury and of severe cutaneous burn injury so that the CBV value decreased to less than two-thirds of control value. An improved urinary response to fluid infusion and cessation in edema formation achieved 24 to 48 hours after injury suggested termination of the resuscitation phase, but even at this phase, a decrease in CBV still remained in hypovolemic status. The foregoing values of conventional parameters provided information on the existence of hypovolemia, but they did not reflect the magnitude of hypovolemia.

Although the CBV values obtained by the pulse dye-densitometry method have been validated in healthy normal subjects[13,14,18,19], its validity in critically ill patients is still argued[21]. The ground of the argument arises from suspicion of a leakage of dye throughout the vessel, especially in the "leaky capillary syndrome" of which burns are typical[31]. We are of the belief that the effect of dye leakage on measurement is negligible for the following reasons. It has already been confirmed that up to 80% of injected ICG binds to plasma protein[3]. Yan-Ling He and his coworkers demonstrated a similar distribution volume between ICG completely bound to plasma proteins and free fraction of ICG[14]. Birke reported that by using isotope labeled albumin, maximally 700 g of albumin was observed to leave the circulating blood within 24 hours in a 80% burned patient[7]. As measurement of CBV by pulse dye-densitometry can be completed within 6 minutes, plasma albumin leakage within 6 minutes was calculated to be 3 g at most. Birke also calculated the patient's albumin pool to be 120g. Thus, at most 1/40 of the injected dye is calculated to have leaked during measurement, which is regarded as negligible. Even if enough dye should leak to affect the value, the dye concentration would become lower and CBV values would be calculated as greater than their actual value. The values of CBV measured in critically ill patients even in "leaky capillary syndrome" by the dye-densitometry method may be greater rather than smaller than the true CBV.

One drawback of the procedure is that repeated measurements at once are not possible and thus there is a possibility of an unrefined random measurement error. We carefully treated this problem in this study. Examination of the detection curvature is useful in evaluating the reliability of the value.

Conventionally, we have estimated the amount of blood volume in a patient as one-thirtieth of body weight. In the classical study of Moore using radioisotopes, CBV was calculated to be 6.5% of body weight in female patients and 7% in male patients[26]. Yan-Ling He and his coworkers reported CBV measured by pulse dye-densitometry in healthy volunteers to be 72.6 ± 3.1 ml/kg[14]. The CBV value which we used for control was 76.7 ± 9.0 ml/kg (7.67 ± 0.90% of body weight) and this seemed to be acceptable for standard Japanese adults[12,30].

Recently, a debate has arisen as to where to place the optimal resuscitation endpoint in burn resuscitation. There have been experimental and clinical trials using the values of serum lactate or base deficit or using a pulmonary artery thermodilution catheter with the purpose of balancing oxygen delivery sufficiently for tissue oxygen consumption to prevent hypoxic tissue damage and organ failure. These trials suggested the existence of suboptimal circulatory performance if directed only by the traditional resuscitation formula.

Consistent elevation of the serum lactate level has been reported to be useful in indicating the presence of malperfusion in other critical situations[4,8,24,34]. Jeng et al demonstrated that conventional resuscitation parameters such as urine output, mean arterial pressure and fluid administration rate were low in correlation with serum lactate and base deficit in burn resuscitation and that the values of serum lactate and base deficit provide a reliable guideline in burn resuscitation[22]. In our study, a discrepancy was observed that the similarly decreased CBV of solely inhalation injury patients did not cause a similar elevation in serum lactate compared to cutaneous burns. The probable causes for this discrepancy are a discrepancy in generating lactate[35] (absence or presence of nonviable burned tissue), a discrepancy in circulatory redistribution[16,17,28] or a discrepancy in metabolic alteration[25] between smoke inhalation injury and cutaneous burn. However, this question has not yet been well investigated and requires further study.

The result of this study suggested the magnitude of "unrecognized underresuscitation". A depletion in CBV is similarly observed in solely inhalation injured patients, and is speculated to be a cause of the increased fluid requirement in smoke inhalation injury. From our experience, the attempt to correct the decreased CBV up to control

level was not achieved by fluid replacement and inotropic supports; further aggressive infusion did not seem to recover the state of hypovolemia but only to increase tissue edema or lung edema. It also appeared as if there was a physiological hypovolemic threshold. This deviation in CBV did not seem to terminate until after the first 4 days or one week, or even later. Thus, in view of its useful, non-invasive and convenient nature, we consider that the role of hourly urine output in burn resuscitation should be re-evaluated as one of the practical clues in managing patients within permissive hypovolemia.

The mechanism of the decrease in CBV is not fully understood. Multiple mediators such as histamine, bradykinin, products of arachidonic acid, and oxygen free radicals may play a role in increasing capillary permeability[2]. Lalonde and coworkers assumed that the increased fluid requirements were due to systemic oxidant effects in their experimental study[23]. Demling and his associates, using sheep as experimental subjects in which to study controlled inhalation injury, found evidence of increased oxidant activity at airway surfaces[10]. These changes, unfortunately, did not correspond well in their study with the clinical development of pulmonary dysfunction that appeared later. There are plenty of pathophysiological aspects that require further investigation to elucidate the mechanism[1]. However, we are of the belief that monitoring CBV status and findings will lead to a new pathophysiological understanding in burn patients and patients in critical care.

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