

Intravenous infusion of hyperosmotic NaCl solution induces acute cor pulmonale in anesthetized rats

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Abstract Intravenous hyperosmotic NaCl infusion is an effective treatment for circulatory shock. However, a fast infusion rate (2 mL/kg at the rate of 1 mL/s) induces transient hypotension. This response has been reported to be due to decreased total peripheral resistance and/or decreased cardiac performance. Although the hypotension is transient and recovers within 2 min without detrimental consequences, it is important to understand the associated hemodynamics and mechanisms. We found that the hypotensive effect was larger with intravenous NaCl infusion than with intra-aortic infusion, indicating that change in cardiac performance played a more significant role than change in peripheral resistance. NaCl infusion induced an increase in pulmonary vascular resistance and central venous pressure and a decrease in right ventricular dP/dt max, suggesting acute cor pulmonale. Diastolic ventricular crosstalk-induced left ventricular failure was also observed. Hyperosmotic NaCl-induced hypotension was therefore mainly due to a combination of acute cor pulmonale and left ventricular failure.

Keywords Arterial pressure · Aortic flow · Total systemic peripheral resistance · Left ventricle · Right ventricle · dP/dt max

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Introduction

Rapid intravenous infusion of hyperosmotic NaCl solution is used for resuscitation of circulatory shock [1, 2]. Hyperosmotic NaCl solution is thought to increase arterial pressure (AP) by the following mechanisms. First, hyperosmotic NaCl solution can move interstitial fluid into the intravascular compartment more efficiently than isotonic NaCl solution, thereby contributing to increased venous return [3, 4]. Second, hyperosmotic NaCl solution increases $\text{Na}^+/\text{Ca}^{2+}$ exchange activity, which increases Ca^{2+} influx [5]. Third, hyperosmotic NaCl solution increases Na^+/H^+ exchange activity and reduces intracellular H^+ concentration, which increases binding of Ca^{2+} to troponin C [6]. The increased Ca^{2+} influx and increased binding of Ca^{2+} to troponin C increase cardiac contractility. Kien et al. [7] reported that infusion of hyperosmotic NaCl solution increased cardiac contractility and cardiac output in anesthetized dogs.

Infusion of hyperosmotic NaCl solution at 2–5 mL/kg/min has been used for therapeutic purposes [1]. However, this infusion rate occasionally induces hypotension in animals and humans [2, 7, 8]. Although the hypotension is transient and recovers within 2 min without detrimental consequences, it is important to understand the associated hemodynamics and mechanisms. To investigate this response, we induced severe hypotension by very rapid intravenous infusion of hyperosmotic NaCl solution, as the hypotension occurs in a rate- or concentration-dependent manner [9]. To evaluate the specific effects of infusion on the systemic and pulmonary circulations, hyperosmotic NaCl solution was infused into the inferior vena cava or the ascending aorta. To evaluate the systemic circulation, we measured left ventricular pressure (LVP), AP, central venous pressure (CVP), myocardial blood flow, and aortic

blood flow. To evaluate the pulmonary circulation, we measured right ventricular pressure (RVP), LVP, pulmonary arterial blood flow, and alveolar blood flow.

Methods

Animals

The animals used in the present study were maintained in accordance with the Guiding Principles for Care and Use of Animals in the Field of Physiological Science set by the Physiological Society of Japan. The experiments were approved by the Animal Research Committee of Gifu University. We used male Sprague–Dawley rats (12 weeks old, 360–400 g).

Implantation of catheters

All rats ($n = 42$) were anesthetized with intraperitoneal urethane (500 mg/kg) and α -chloralose (50 mg/kg). Polyethylene catheters (PE-50; Becton–Dickinson, Sparks, MD, USA) were placed in the inferior vena cava via the femoral vein for infusion, in the superior vena cava via the right jugular vein for CVP measurement, in the abdominal aorta via the left femoral artery for AP measurement, and in the left ventricle via the right common carotid artery for LVP measurement. For RVP measurement, the tip of the catheter was placed in the right ventricle instead of the superior vena cava. Mechanical ventilation (SAR830/P; CWE, Ardmore, PA, USA) was administered via a tracheal tube using room air. Pancuronium bromide (Myoblock; Sankyo, Tokyo, Japan) was injected intravenously (0.08 mg/kg) depending on involuntary movements. Body temperature was maintained at 37 °C with a heating pad.

Effects of infusion of 9 % NaCl solution on the systemic circulation ($n = 30$)

To examine the effects of rapid infusion of 9 % NaCl solution on the systemic circulation, we conducted the

Table 1 Mean \pm SEM of arterial pressure (AP), heart rate (HR), central venous pressure (CVP), left ventricular developed pressure (LVDP), left ventricular end-diastolic pressure (LVEDP), positive dP/dt max, and negative dP/dt max for each group just before intravenous infusion of each solution

	Water	0.9 %	3 %	6 %	9 %
AP (mmHg)	114 \pm 6.1	112 \pm 1.9	116 \pm 2.1	118 \pm 2.1	121 \pm 3.7
HR (beats/min)	413 \pm 18.6	433 \pm 17.7	437 \pm 13.9	432 \pm 11.9	415 \pm 5.1
CVP (mmHg)	2 \pm 0.1	2 \pm 0.2	2 \pm 0.1	2 \pm 0.2	2 \pm 0.1
LVDP (mmHg)	165 \pm 8.4	147 \pm 1.3	149 \pm 6.6	145 \pm 4.8	149 \pm 2.7
LVEDP (mmHg)	2 \pm 0.2	2 \pm 0.2	3 \pm 0.1	2 \pm 0.1	2 \pm 0.1
Positive dP/dt max	17,755 \pm 1,323.6	14,538 \pm 997.4	14,692 \pm 819.5	14,944 \pm 886	16,446 \pm 1,370.5
Negative dP/dt max	-7,499 \pm 560.4	-7,077 \pm 242.3	-7,298 \pm 301.8	-7,192 \pm 143.1	-7,170 \pm 219.8

following five experiments. First, the dose-dependent effect of infusion of hyperosmotic NaCl solution was examined ($n = 6$). While measuring LVP, AP, CVP, and dP/dt max, distilled water or NaCl solution (0.9, 3, 6, or 9 %) was rapidly infused into the vena cava (2 mL/kg at a rate of 1 mL/s) using a syringe pump (KDS220; Holliston, MA, USA). The infusion sequence was random. Second, the response of total systemic peripheral resistance to rapid intravenous infusion of 9 % NaCl solution was examined ($n = 6$). The total systemic peripheral resistance was calculated by dividing the pressure gradient between mean AP and mean CVP by mean aortic flow. Aortic flow was measured using a transit-time flowmeter (TS420; Transonic Systems, Ithaca, NY, USA). The probe of the flowmeter was attached to the ascending aorta after thoracotomy. Third, the participation of the autonomic nervous system in the rapid intravenous infusion of 9 % NaCl solution was examined ($n = 6$). We compared LVP, AP, and CVP in response to 9 % NaCl solution before and after the administration of hexamethonium bromide (60 mg/kg; Sigma-Aldrich, St. Louis, MO, USA). Fourth, the effect of intra-aortic infusion of 9 % NaCl solution on AP was examined and was compared with the response to intravenous infusion ($n = 6$). And fifth, the response of myocardial blood flow to infusion of 9 % NaCl solution was examined ($n = 6$). Myocardial blood flow was measured using laser-Doppler flowmetry (model FLO-C1 BV; Omegawave, Tokyo, Japan). The flow probe consisted of two glass fibers: one to introduce the laser light and the other to detect the reflection. The tips of the fibers were glued so that they were 0.5 mm apart, and were attached to the surface of the left ventricular myocardium after thoracotomy.

Effects of infusion of 9 % NaCl solution on the pulmonary circulation ($n = 12$)

To examine the effects of rapid intravenous infusion of 9 % NaCl solution on the pulmonary circulation, pulmonary vascular resistance was calculated as the pressure dt max, and negative dP/dt max for each group just before intravenous infusion of each solution

gradient between mean RVP and mean LVEDP divided by the mean pulmonary arterial blood flow ($n = 6$). The pulmonary arterial blood flow was measured by Doppler sonography using a VEVO-770TTM Micro-Imaging System (Visual Sonic, Toronto, ON, Canada) equipped with a 15-MHz transducer. Mean pulmonary arterial blood flow was calculated as the product of the pulmonary artery diameter and the mean flow velocity. The dP/dt max of RVP was calculated at its lowest point. Alveolar blood flow

was measured using the same method as measurement of myocardial blood flow ($n = 6$). Responses of these variables to intravenous infusion of 9 % NaCl solution (2 mL/kg at a rate of 1 mL/s) were examined.

Data collection and analysis

LVP, AP, RVP, and CVP were measured using a catheter connected to a pressure transducer (MP5200; Baxter, Deerfield, IL, USA). The signal from the transducer was transmitted to an amplifier (MEG-6108; Nihon Kohden, Tokyo, Japan). All signals were recorded using an analog-to-digital converter (PowerLab; AD Instruments, Bella Vista, Australia) at a rate of 1,000 Hz. The 10-s averaged values of the maximum response of left ventricular developed pressure (LVDP), left ventricular end-diastolic pressure (LVEDP), AP, and CVP were compared with their 30-s averaged baseline values. Maximum positive or negative dP/dt was calculated from the LVP data. For total systemic peripheral resistance, myocardial blood flow, and alveolar blood flow, 10-s averaged values were calculated from 30 s before to 120 s after the infusion. For myocardial and alveolar blood flow, the values are presented as a percentage, with 100 % set as the 30-s averaged values measured just before the infusion.

All data are presented as mean \pm standard error of the mean. Significant differences between pairs of groups were determined using paired t test, while those between multiple groups were determined using one-factor repeated measures ANOVA. If the F ratio indicated statistical significance, the Tukey–Kramer post hoc test was applied for within-group comparisons. For the post hoc test, the significance level was set at $P < 0.05$.

Results

There were no significant differences in baseline AP, HR, CVP, LVDP, or LVEDP values for different infusion types (Table 1). Rapid intravenous infusion of 0.9 % NaCl solution did not change LVP, AP, or CVP (Fig. 1a). However, rapid intravenous infusion of 9 % NaCl solution resulted in a decrease in LVDP and AP and an increase in LVEDP and CVP (Fig. 1b). This response was substantially different from the response to slow infusion of 9 % NaCl solution at a rate of 1 mL/kg/min (Fig. 1c). The hemodynamic responses to infusion of hyperosmotic NaCl solutions are shown in Fig. 2. LVDP and LVEDP were obtained from the LVP waveform. Concentration-dependent decreases in LVDP and AP started with infusion of 3 % NaCl solution, but this concentration had no effect on LVEDP or CVP. Both positive and negative dP/dt max were decreased in a concentration-dependent manner with

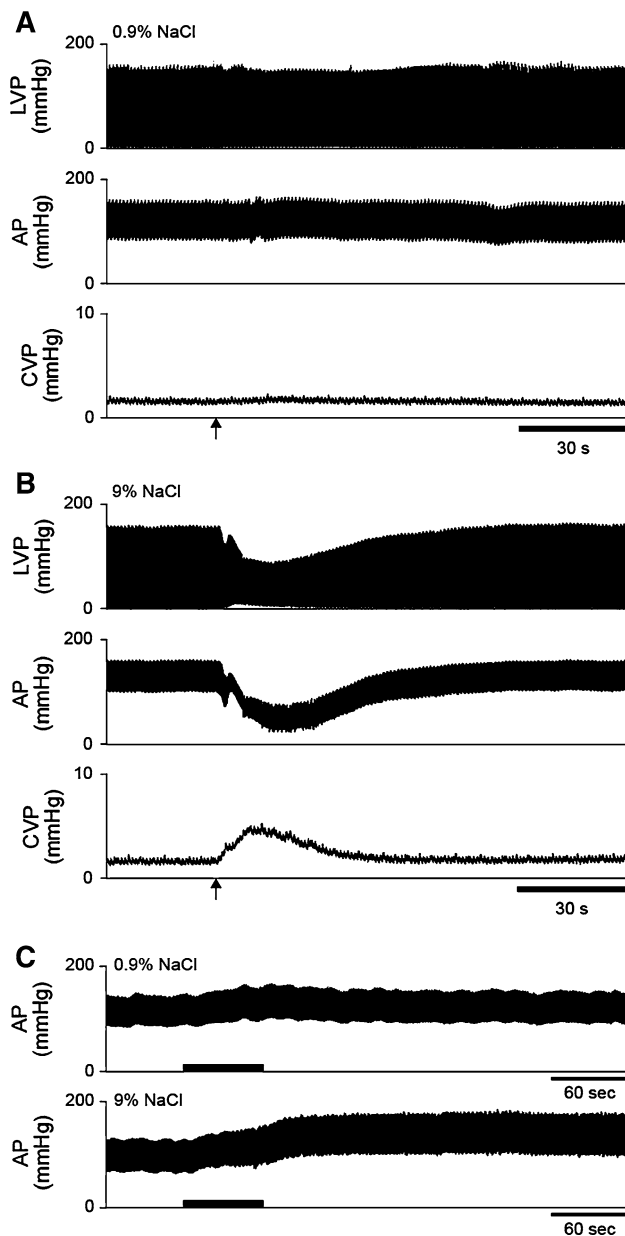


Fig. 1 a Typical recordings of left ventricular pressure (LVP), arterial pressure (AP), and central venous pressure (CVP) in response to rapid infusion (2 mL/kg, 1 mL/s) of 0.9 % NaCl solution. b Typical recordings of LVP, AP, and CVP in response to rapid infusion (2 mL/kg, 1 mL/s) of 9 % NaCl solution. c Typical recordings of AP in response to slow infusion (2 mL/kg, 0.5 mL/min) of 0.9 or 9 % NaCl solution

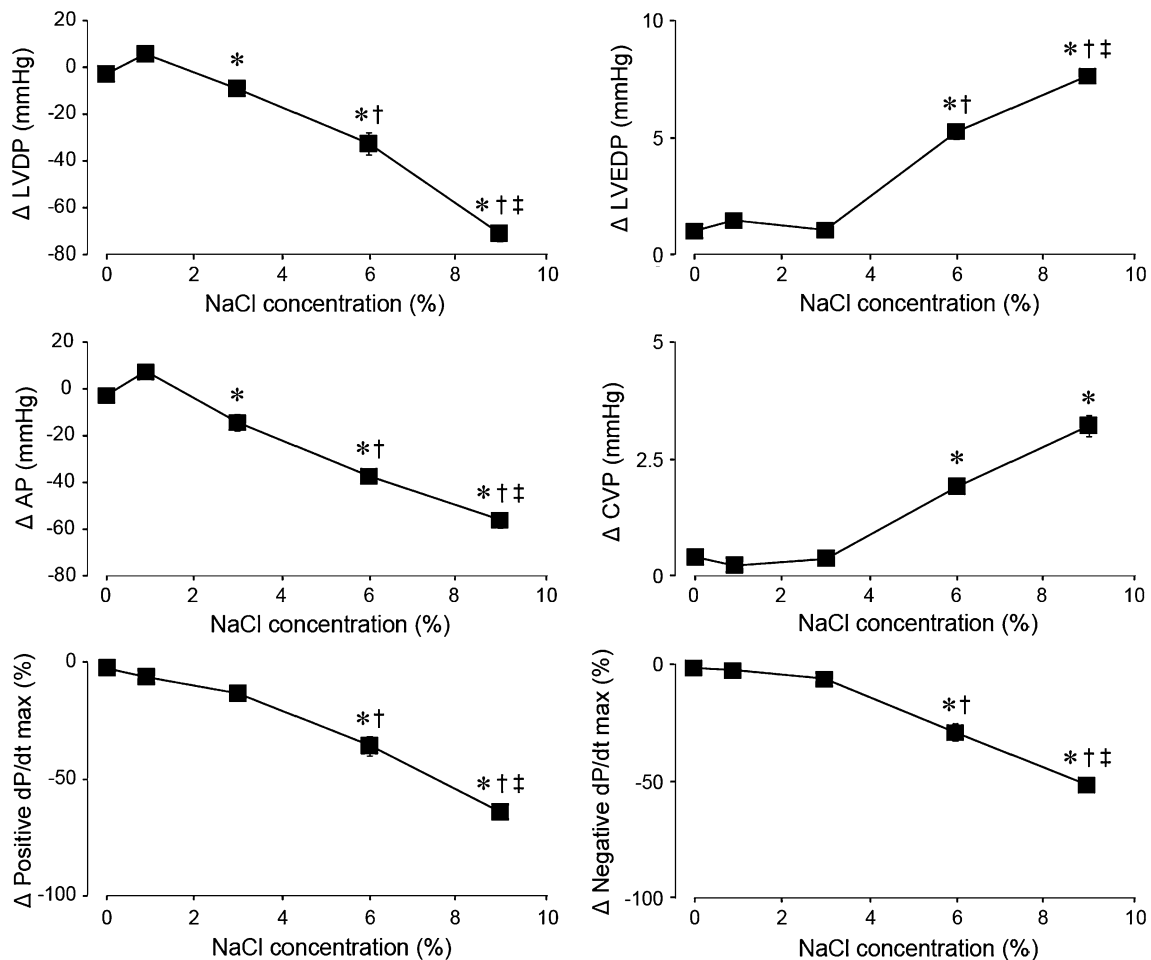


Fig. 2 Changes in left ventricular developed pressure (LVDP), left ventricular end-diastolic pressure (LVEDP), arterial pressure (AP), central venous pressure (CVP), positive dP/dt max, and negative dP/dt max in response to infusion of distilled water and 0.9, 3, 6, and 9 %

NaCl solution. * $P < 0.05$ versus distilled water and 0.9 % NaCl solution, † $P < 0.05$ versus 3 % NaCl solution, ‡ $P < 0.05$ versus 6 % NaCl solution

infusion of 6 and 9 % NaCl solution. These changes recovered within 2 min (Figs. 1c, 3a). Aortic flow was decreased by intravenous infusion of 9 % NaCl solution (Fig. 3a). Total peripheral resistance had a biphasic response to intravenous infusion of 9 % NaCl solution, with an initial increase lasting 20 s followed by a decrease lasting 40 s (Fig. 3b). Although the baseline AP was significantly decreased by hexamethonium bromide administration (121 ± 7 vs. 89 ± 5 mmHg), hexamethonium did not alter the responses of LVDP, LVEDP, AP, CVP, and dP/dt max. Intra-aortic infusion of 9 % NaCl solution resulted in a significant decrease in AP, but this decrease was significantly smaller than the decrease after intravenous infusion (Fig. 3c).

The effects of rapid intravenous infusion of 9 % NaCl solution on right ventricular hemodynamics are shown in Fig. 4. A transient increase in RVP was observed just after infusion, followed by a decrease in right ventricular

developed pressure and an increase in right ventricular end-diastolic pressure (Fig. 4a). Infusion of 9 % NaCl solution resulted in a decrease in peak flow velocity in the pulmonary artery (Fig. 4a), an increase in pulmonary perfusion pressure (difference between mean RVP and mean LVEDP) (Fig. 4b), a decrease in mean pulmonary arterial flow (Fig. 4c), and an increase in calculated pulmonary vascular resistance (Fig. 4d). Positive and negative dP/dt max of RVP were significantly decreased by infusion of 9 % NaCl, but not by infusion of 0.9 % NaCl (Fig. 4e). These values returned to the baseline level within 2 min (Fig. 4a).

A representative response of myocardial blood flow is shown in Fig. 5a. Blood flow decreased just after infusion of 9 % NaCl solution and recovered within 2 min. Recovery of myocardial blood flow preceded recovery of AP. The responses of myocardial and alveolar blood flow are shown in Fig. 5b. Recovery of blood flow to the alveoli was faster than recovery of blood flow to the myocardium.

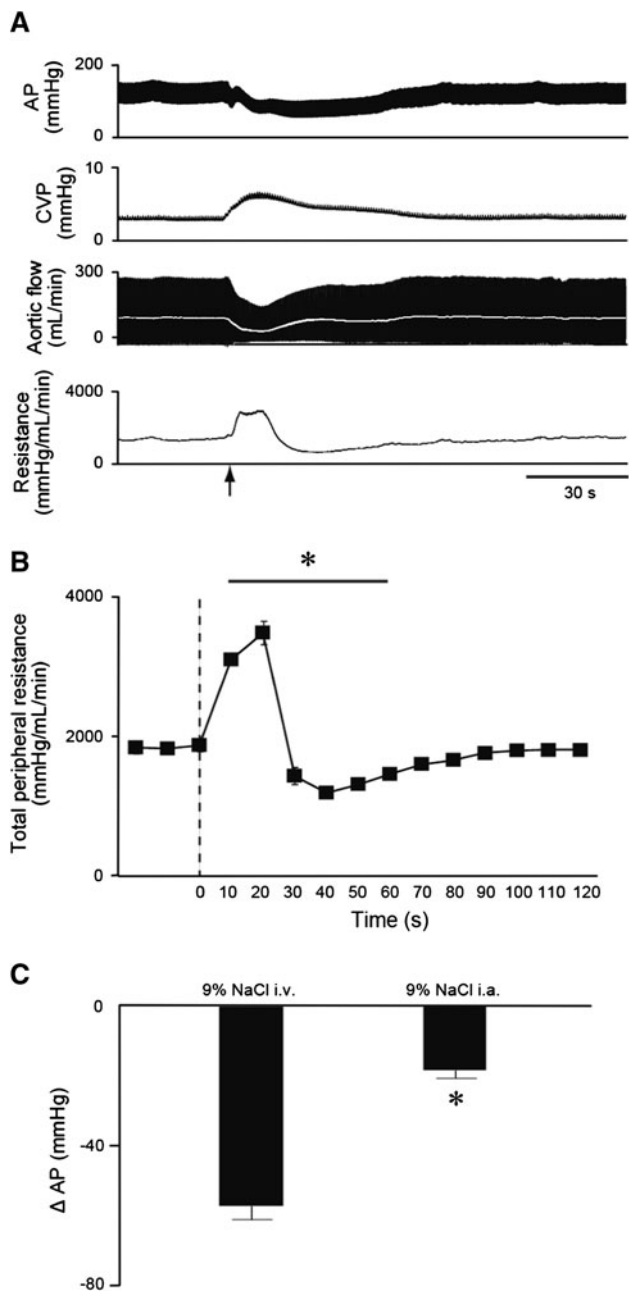


Fig. 3 **a** Typical recordings of arterial pressure (AP), central venous pressure (CVP), aortic flow, and total systemic peripheral resistance in response to rapid infusion (2 mL/kg, 1 mL/s) of 9 % NaCl solution. The arrow indicates the time of infusion. White line in aortic flow indicates mean value. **b** Changes in total systemic peripheral resistance in response to rapid infusion (2 mL/kg, 1 mL/s) of 9 % NaCl solution. The dashed line indicates the time of infusion. **P* < 0.05 versus pre-infusion. **c** Change in AP induced by the intravenous infusion (i.v.) or intra-aortic infusion (i.a.) of 9 % NaCl solution. **P* < 0.05 versus 9 % NaCl i.v

The four-chamber view on echocardiography showed that the interventricular septum was deflected towards the left ventricle just after intravenous infusion of 9 % NaCl

solution (online movie), and had returned to normal within 120 s after the infusion.

Discussion

Rapid intravenous infusion of hyperosmotic NaCl solution induced significant but transient hemodynamic changes in the pulmonary and systemic circulations. The major findings of the present study were as follows: (1) more severe hypotension was observed with intravenous infusion than intra-aortic infusion; (2) rapid intravenous infusion of hyperosmotic NaCl solution resulted in concentration-dependent decreases in LVDP, AP, and left and right ventricular *dP/dt* max, and increased LVEDP and CVP; (3) total systemic peripheral resistance showed a biphasic response to rapid intravenous infusion of hyperosmotic NaCl solution, with an initial increase followed by a decrease; and (4) rapid intravenous infusion of hyperosmotic NaCl solution resulted in increased pulmonary vascular resistance.

Kien et al. [7] examined mechanisms of intravenous hyperosmotic NaCl-induced hypotension in dogs. They observed a reduced total systemic peripheral resistance, and concluded that peripheral vasodilation was a main cause of the hypotension. However, they also observed an increase in LVEDP and a decrease in left ventricular *dP/dt*, suggesting that the hyperosmotic NaCl solution also affected ventricular performance. We evaluated the effects of hyperosmotic NaCl infusion on the heart and systemic circulation, and found that the hypotensive effect was larger after intravenous infusion than after intra-aortic infusion, this was supported by the previous study [8]. It is therefore likely that change in cardiac performance played a more significant role in hyperosmotic NaCl-induced hypotension than change in peripheral resistance.

In the present study, a biphasic response was observed in total systemic peripheral resistance, with an initial transient increase followed by a decrease. Previous studies reported a decrease in total peripheral resistance, but not an initial increase [7, 9, 10]. This is probably due to different infusion rates. In previous studies, the infusion rate was 2–3 mL/kg/30–60 s (7.5 % NaCl or 50 % glucose) in dogs [7, 10] or 0.1 mL/s (7.5 % NaCl) in rats [9], while 2 mL/kg of 9 % NaCl solution was infused at the rate of 1 mL/s in the present study. A higher osmolality or infusion rate might be required to induce the initial increase in total systemic peripheral resistance. Since the hexamethonium bromide administration did not alter the hyperosmotic solution-induced responses, neural mechanisms might not participate in the alteration of the total systemic peripheral resistance.

Read et al. [11] conducted microscopic observation of the perfused hind limb in dogs, and reported that

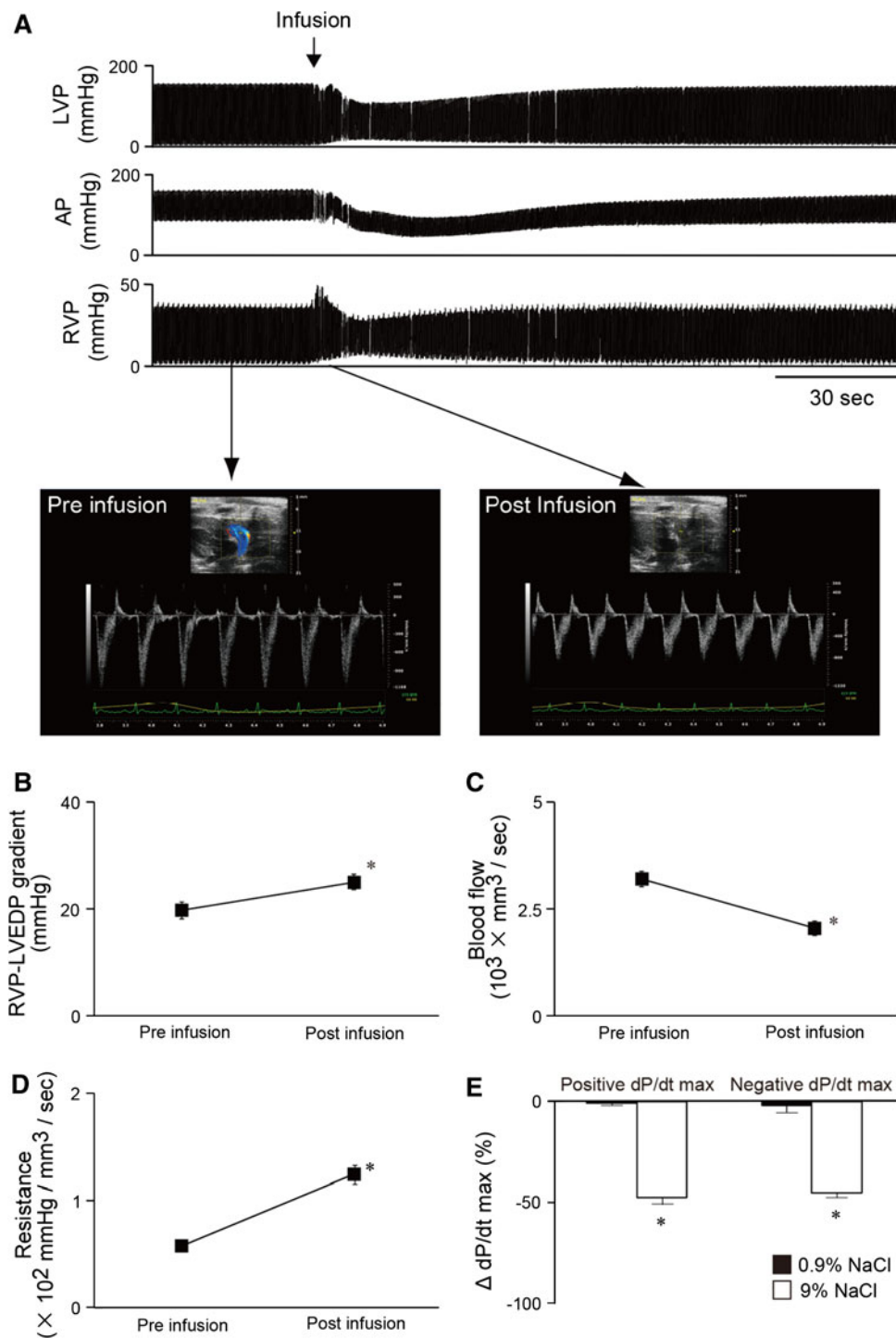


Fig. 4 a Typical recordings of left ventricular pressure (LVP), arterial pressure (AP), and right ventricular pressure (RVP) in response to rapid infusion (2 mL/kg, 1 mL/s) of 9 % NaCl solution. Doppler echocardiography images show blood velocity in the pulmonary artery before (Pre-infusion) and after (Post-infusion) rapid infusion of 9 % NaCl solution. Changes in the mean pressure difference between right ventricular pressure and the left atrium (b), mean pulmonary blood flow (c), and mean resistance in the pulmonary circulation (d) before

(Pre-infusion) and after (Post-infusion) rapid infusion (2 mL/kg, 1 mL/s) of 9 % NaCl solution. * $P < 0.05$ versus pre-infusion. e Changes in positive and negative dP/dt max before (pre-infusion) and after (post-infusion) rapid infusion (2 mL/kg, 1 mL/s) of 0.9 % (solid bar) or 9 % NaCl (open bar) solution. * $P < 0.05$ versus pre-infusion

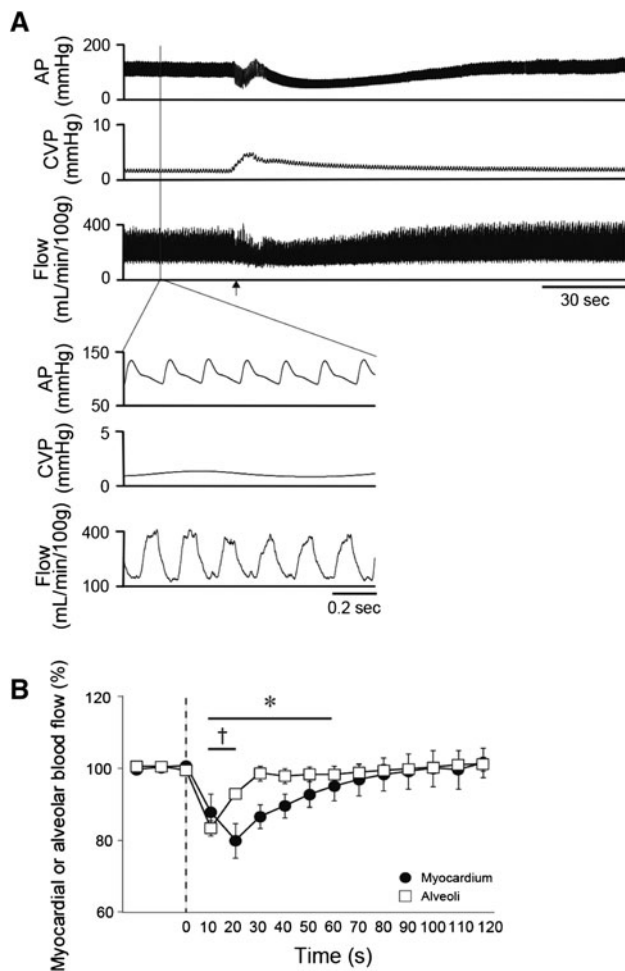


Fig. 5 **a** Typical recordings of AP, CVP, and myocardial blood flow to infusion (1 mL/s) of 9 % NaCl solution. **b** Averaged changes in mean blood flows in the myocardium and the alveoli in response to infusion 9 % NaCl solution. * $P < 0.05$ versus pre-infusion

intra-arterial infusion of hyperosmotic NaCl solution induced aggregation of red blood cells, and that blood flow through the arterioles stopped with a concomitant increase in perfusion pressure. Re-establishment of blood flow occurred within 30–60 s and was accompanied by vasodilation. These responses were completely abolished if the perfusate was changed from whole blood to oxygenated plasma. This biphasic response of the perfused hind limb—stasis of blood flow and vasodilation—may explain our observation of a biphasic response in total systemic peripheral resistance. Their findings also suggest that the increase in pulmonary vascular resistance observed in the present study might be due to aggregation of red blood cells in the pulmonary vasculature. As we measured pulmonary blood flow using Doppler ultrasonography and the maximum continuous recording time was 10 s, we were not able to estimate time-dependent changes in pulmonary resistance. However, it is possible that the pulmonary vasoconstriction

was followed by vasodilation as seen in the systemic circulation and perfused hind limb in the study by Read et al. [11]. This supported our observation that the alveolar blood flow decreased just after the infusion but recovered to the pre-infusion level within 30 s.

In this study, rapid intravenous infusion of hyperosmotic solution induced acute cor pulmonale, with an increase in pulmonary vascular resistance and enlargement of the right ventricle. Acute cor pulmonale is known to decrease left ventricular preload, due to both reduced forward flow in the pulmonary circulation and direct compression of the left ventricular cavity by the dilated right ventricle, and subsequently to reduce left ventricular function via the Frank–Starling mechanism [12–16]. This phenomenon is known as diastolic ventricular crosstalk. Echocardiographic observations confirm this phenomenon of the dilated right ventricle compressing the left ventricle. Compliance of the compressed left ventricle might decrease [15], resulting in an increase in LVEDP in spite of the decreased preload. Acute right ventricular failure-induced acute left ventricular failure therefore also played a role in the hyperosmotic NaCl solution-induced hypotension. Since recovery of aortic flow and myocardial blood flow were delayed compared with alveolar blood flow, functional recovery of the right ventricle might be faster than that of the left ventricle.

In conclusion, slow infusion of 9 % NaCl solution was effective for increasing AP compared with slow infusion of 0.9 % NaCl solution. However, a higher infusion rate or osmolality carries a risk of inducing acute cor pulmonale and subsequent left ventricular failure, even if the infusion volume is unchanged.

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Conflict of interest None.

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