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Distinctive effect of 6% hydroxyethyl starch 130/0.4 (Voluven) infusion on pediatric patients with congenital heart disease

J.-Z. ZHANG[1], J.-S. LIU[2], S.-H. ZHANG[1], S.-Y. HUANG[3], J.-J. ZHANG[4], J. ZHOU[4], J.-H. ZHOU[5]

[1]Department of Anesthesia, Yantaishan Hospital, Yantai, Shandong, China
[2]Department of Anesthesia, Dongying City People's Hospital, Dongying, Shandong, China
[3]Department of Oncology, Yantaishan Hospital, Shandong, China
[4]Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC, USA
[5]Institute for Tumor Immunology, Ludong University School of Life Sciences, Yantai, Shandong, China

Jianzhong Zhang and Jinshan Liu contributed equally to this work

Abstract. – OBJECTIVE: It has not been clear that Voluven (6% hydroxyethyl starch 130/0.4) may be administered in pediatric patients safely. The purpose of this study was to determine if Voluven could be used for blood volume expansion and hypovolemia prevention in pediatric patients with congenital heart disease.

PATIENTS AND METHODS: 50 pediatric patients with congenital heart disease were recruited in the study. Circulatory and respiratory parameters were determined to monitor the responses to intravenous infusion of Voluven in the patients.

RESULTS: Intravenous infusion of Voluven significantly increased levels of colloid osmotic pressure and central venous pressure, but decreased levels of hemoglobin in the patients. Voluven infusion did not significantly affect colloid osmotic pressure, central venous pressure, hemoglobin and heart rate in the preschool children (<6 years old), and similarly, low infusion (100-240 mL per patient) of Voluven did not significantly affect colloid osmotic pressure, central venous pressure, hemoglobin and heart rate in the young child patients. Also, there was the similar response, i.e. increased colloid osmotic pressure, to Voluven infusion in both female child patients and patients with atrial septal defect.

CONCLUSIONS: Voluven may be used in pediatric patients with congenital heart disease, but not in the preschool child patients. Furthermore, special attention should be paid to the intravenous administration of Voluven for blood volume expansion and hypovolemia prevention in female pediatric patients and child patients with atrial septal defect.

Key Words:
Voluven, Congenital heart disease, Colloid osmotic pressure, Central venous pressure, Hemoglobin.

Abbreviations

ASD = atrial septal defect; VSD = ventricular septal defect

Introduction

Voluven is the trade name for 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection[1]. Hydroxyethyl starch 130/0.4 represents the mean molecular weight of 130,000 daltons and the molar substitution of 0.4 by hydroxyethyl groups on glucose units of the starch[2]. Voluven can expand plasma volume when it is administered intravenously[3]. It is one of the most common substitutes used for volume expansion, hypovolemia prevention and acute normovolemic hemodilution[3-5]. Voluven is also often used to prevent shock due to severe blood loss caused by surgery for adult and pediatric patients with congenital heart disease. The results from the clinical trials of Voluven appeared to be conflicting. It has been reported that the intravenous administration of Voluven in critically ill patients requiring volume resuscitation has a greater risk of acute kidney injury and death as compared with other intravenous solutions such as dextrans, gelatins and human albumin[6]. Therefore, Voluven could not be used in adult septic patients undergoing open heart surgeries in association with cardiopulmonary bypass due to excess bleeding[7]. It is also not clear that Voluven may be administered in pediatric patients safely. Recently, a case report[8] indicated that successful surgical repair of a ventricular septal defect

Corresponding Author: Juhua Zhou, Ph.D; e-mail: m18153529929@163.com

utilizing Voluven for autologous normovolemic hemodilution in a Jehovah's Witness child was achieved. The result suggests that Voluven may be used in pediatric patients requiring surgical repair of congenital heart disease. In this study, we investigated the effects of Voluven infusion on 50 Chinese pediatric patients receiving surgical repair of congenital heart disease.

Patients and Methods

Patients and Patient Treatment

This clinical trial was approved by the Institutional Review Board of Yantaishan Hospital and registered in the Chinese Clinical Trial Registry (the clinical trial registration No. ChiCTR-IPR-15006963). This study was also approved by the Ethics Committee of Yantaishan Hospital to protect the interests of patients and address moral issues. Written informed consent was obtained by the signature of parents of pediatric patients under the age of 16 years or by the signature of pediatric patients over the age of 16 years preoperatively. The research background, purpose, procedures, risk and benefits of the clinical trial were thoroughly discussed with pediatric patients and their parents. Enough time was given to the participants for their considering carefully. Contact information for addressing any questions was provided to the participants. Written consent to publish the demographic and clinical data was also obtained from all of the participated pediatric patients and signed by the parents of pediatric patients under the age of 16 years or pediatric patients over the age of 16 years. 50 pediatric patients with congenital heart disease were recruited in this study for plasma volume expansion with Voluven and surgical repair of atrial and ventricular septal defect (Tables I). The heights and weights of pediatric patients were measured and the blood volume for each patient was calculated. 5 $\mu g \cdot kg^{-1}$ fentanyl, 100 $\mu g \cdot kg^{-1}$ midazolam, 100 $\mu g \cdot kg^{-1}$ pipecuronium bromide and 1 $mg \cdot kg^{-1}$ propofol were used to anesthetize pediatric patients by intravenous administration. Then, 10% blood volume of Voluven (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride) were infused into the patients at the speed of 0.5 $mL \cdot kg^{-1} \cdot min^{-1}$ through the peripheral vein. 30 min after the finish of Voluven infusion, the surgical repair of ventricular septal defect and atrial septal defect in pediatric patients was carried out.

Measurement of Circulatory and Respiratory Parameters

Colloid osmotic pressure of plasma samples and hemoglobin concentration in the blood samples from the pediatric patients were determined prior to the Voluven infusion, and at 15 min and 30 min after the finish of Voluven infusion using Wescor 4420 Colloid Osmometer (Wescor Inc., Logan, UT, USA) and Sysmex KX-21 Hematology Analyzer (*Japan* System *Care Co., Ltd.,* Shinagawa-ku, Japan). Heart rate, mean arterial pressure, central venous pressure, airway pressure, peak inspiratory pressure, plateau inspiratory pressures, positive end-expiratory pressure and vascular compliance of pediatric patients were measured using a standard anesthetic machine (Datex Ohmeda Excel 210 SE, SOMA Technology, Inc., Bloomfield, CT, USA) with a semi-closed circle absorber system at three time points, prior to the Voluven infusion (T0), the infusion of half volume of Voluven (T1/2), and the finish of Voluven infusion (T1).

Statistical Analysis

Data were expressed as mean ± SEM. Statistical analyses were performed using SPSS13.0 software (SPSS Inc. Chicago, IL, USA). Statistical differences between different groups of patients were determined using Student's *t*-test and statistical differences between different parameters in the same group of patients were determined using the two-way ANOVA. Multiple comparisons between the groups were performed using the Student-Neuman-Keuls test. p-value <0.05 was considered statistically significant.

Results

Effect of Voluven Infusion on Circulatory and Respiratory Functions

Fifty Chinese pediatric patients with congenital heart disease were enrolled in the study. The ages of patients were between 2 years and 17 years. Among the patients, there were 22 girls and 28 boys. 19 patients had atrial septal defect (ASD) and 31 patients had ventricular septal defect (VSD). The patient demographic data were shown in Table I. Colloid osmotic pressure, which is determined by proteins such as albumin in blood plasma, maintains the proper levels of liquid in the body tissues and avoid escaping of too much liquid from the capillaries. Central venous pressure, the pressure of blood in the thoracic vena

Table I. Demographics of pediatric patients for Hydroxyethyl Starch infusion.

Patient ID	Gender*	Age (Year)	Height (Meter)	Weight (kg)	Disease**	Infusion of Hydroxyethyl Starch (L)
YTS1	F	17	1.63	65.0	VSD	0.50
YTS2	M	12	1.50	38.5	ASD	0.30
YTS3	F	13	1.58	48.0	VSD	0.38
YTS4	M	13	1.53	38.5	ASD	0.30
YTS5	F	15	1.50	44.0	ASD	0.35
YTS6	M	16	1.70	60.5	VSD	0.47
YTS7	M	13	1.55	43.0	ASD	0.33
YTS8	M	15	1.66	52.5	VSD	0.40
YTS9	M	15	1.57	48.0	VSD	0.40
YTS10	M	12	1.42	32.0	VSD	0.25
YTS11	M	13	1.60	41.5	ASD	0.31
YTS12	F	13	1.55	39.0	VSD	0.30
YTS13	M	12	1.55	45.0	VSD	0.35
YTS14	M	9	1.34	30.0	ASD	0.24
YTS15	F	16	1.68	62.0	VSD	0.48
YTS16	F	15	1.58	48.0	VSD	0.36
YTS17	M	10	1.38	31.0	VSD	0.25
YTS18	M	17	1.65	49.0	VSD	0.38
YTS19	M	8	1.32	34.5	ASD	0.27
YTS20	M	15	1.63	42.5	ASD	0.32
YTS21	M	12	1.55	45.5	VSD	0.35
YTS22	F	10	1.43	32.0	VSD	0.25
YTS23	M	17	1.75	60.0	VSD	0.45
YTS24	F	10	1.42	35.0	VSD	0.27
YTS25	F	17	1.54	38.0	ASD	0.30
YTS26	F	9	1.36	33.0	VSD	0.25
YTS27	F	13	1.63	53.0	VSD	0.40
YTS28	F	10	1.38	28.0	ASD	0.21
YTS29	F	15	1.60	54.0	ASD	0.42
YTS30	M	14	1.63	54.0	VSD	0.40
YTS31	M	5	1.17	22.0	VSD	0.17
YTS32	F	5	1.07	17.0	ASD	0.12
YTS33	M	2	0.89	12.0	VSD	0.10
YTS34	F	3	1.01	16.0	VSD	0.12
YTS35	F	5	1.14	21.0	VSD	0.16
YTS36	F	4	1.08	17.0	VSD	0.13
YTS37	M	5	1.14	16.5	ASD	0.13
YTS38	M	5	1.13	19.0	VSD, ASD	0.15
YTS39	M	6	1.20	20.0	VSD	0.15
YTS40	M	6	1.25	26.5	VSD	0.20
YTS41	M	2	0.96	15.0	ASD	0.12
YTS42	M	6	1.10	19.5	VSD	0.15
YTS43	F	5	1.22	22.0	ASD	0.18
YTS44	M	4	1.17	18.0	VSD	0.14
YTS45	F	3	1.06	17.5	ASD	0.14
YTS46	M	4	1.08	18.5	ASD	0.15
YTS47	F	4	1.07	18.5	VSD	0.15
YTS48	M	5	1.15	20.0	ASD	0.16
YTS49	F	6	1.24	22.0	ASD	0.17
YTS50	F	10	1.37	34.8	VSD	0.27

*F, female; M, male. **ASD, atrial septal defect; VSD, ventricular septal defect.

cava, near the right atrium of the heart, determines the capability of heart to drive the blood into the arterial system and the amount of blood going back to the heart. Monitoring colloid osmotic pressure and central venous pressure is usually used to observe the volume-responsiveness to infusions of intravenous fluid[9,10]. We thus were interested in examining the effects of Voluven

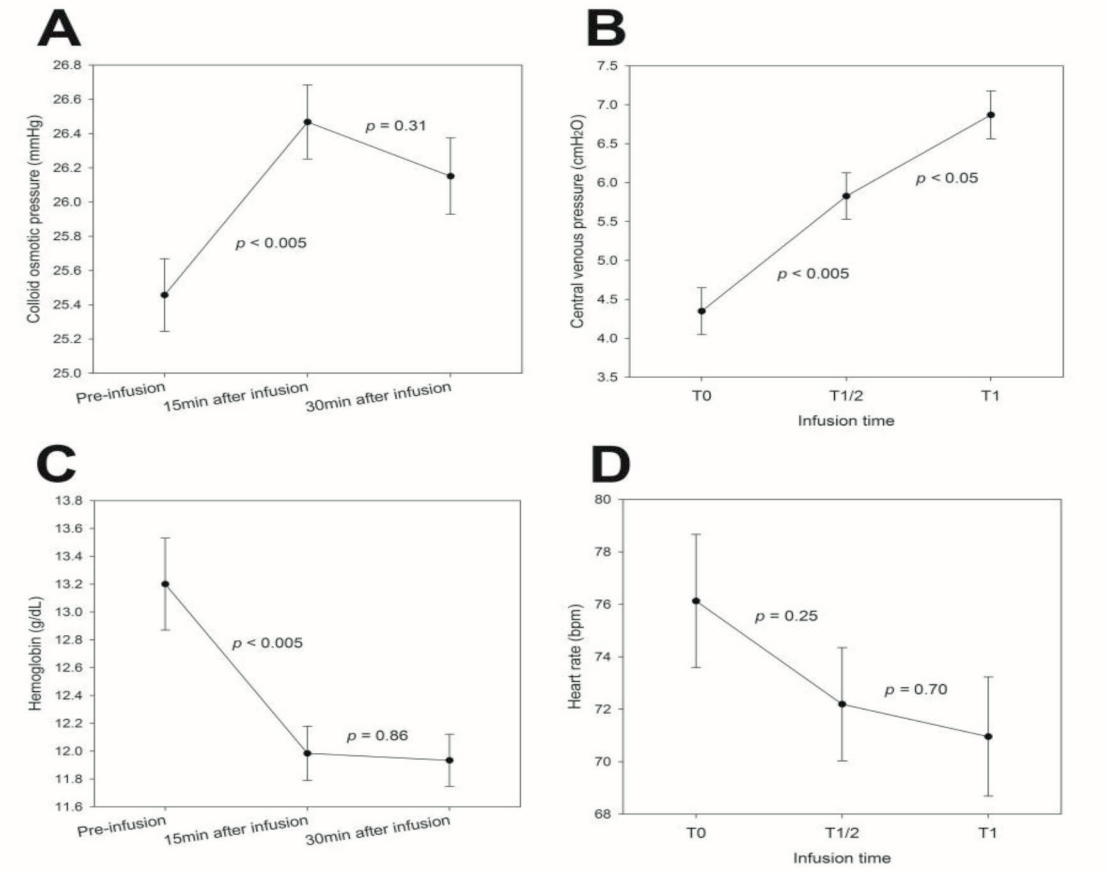


Figure 1. Changes of circulatory parameters in response to Voluven infusion in pediatric patients with congenital heart disease. Voluven was intravenously administrated in the patients. Colloid osmotic pressure ***(A)*** and hemoglobin ***(C)*** were measured prior to the Voluven infusion, and at 15 min and 30 min after the finish of Voluven infusion. Central venous pressure ***(B)*** and heart rate ***(D)*** were monitored prior to the Voluven infusion (T0), the infusion of half volume of Voluven (T1/2), and the finish of Voluven infusion (T1).

infusion on colloid osmotic pressure and central venous pressure as well as hemoglobin and heart rate in pediatric patients with congenital heart disease, who required Voluven infusion for open-heart surgery repair. Our studies discovered that intravenous infusion of Voluven significantly induced the increase of colloid osmotic pressure (Figure 1A) and central venous pressure (Figure 1B), but brought about the decrease of hemoglobin in the patients (Figure 1C); however, it did not significantly affect the heart rate (Figure 1D) and the other circulatory and respiratory parameters such as airway pressure, peak inspiratory pressure, positive end-expiratory pressure and vascular compliance of pediatric patients (Additional Figures 1, 2 and 3). The results indicated that Voluven may be used in pediatric patients with congenital heart disease for volume expansion and hypovolemia prevention.

Effect of Age Factor on Voluven Infusion

It has been shown that age was a factor associated with physiological status and disease occurrence in children[11]. Since Voluven infusion could increase colloid osmotic pressure and central venous pressure, but decrease hemoglobin in pediatric patients with congenital heart disease (Figure 1), we next determine the effect of age factor on Voluven infusion in pediatric patients. For this purpose, two groups of children, i.e. preschool children (<6 years old) and teenagers (>12 years old), were selected to compare with the elder children (>6 years old) and young children (<12 years old) in response to Voluven infusion, respectively. It was surprising to find out that intravenous administration of Voluven did not significantly affect colloid osmotic pressure, central venous pressure, hemoglobin and heart rate in the preschool children; however, it significantly increased col-

loid osmotic pressure and central venous pressure, and decreased hemoglobin in the elder child patients (Figure 2). Differently from the situation in preschool children, the teenagers had the similar responses to Voluven infusion as the young children (Figure 3). The results suggested that age factor influenced the effect of Voluven infusion for volume expansion and hypovolemia prevention in pediatric patients. Although intravenous infusion of Voluven did not significantly affect airway pressure, peak inspiratory pressure, positive end-expiratory pressure and vascular compliance of pediatric patients, the preschool child patients had higher levels of airway pressure, peak inspiratory pressure and positive end-expiratory pressure, but lower levels of vascular compliance (Additional Figure 1). Differently, the teenage patients only had higher levels of airway pressure and lower levels of vascular compliance, and there were not significant differences in peak inspiratory pressure and positive end-expiratory pressure between the teenage patients and young child patients (Additional Figure 2). These results indicated that the preschool child patients might have unique physiological features, which may be responsible for the effect of Voluven infusion for volume expansion and hypovolemia prevention in the pediatric patients (Figure 2).

Effect of Infusion Volume on Voluven Administration

The infusion volume for Voluven administration in pediatric patients with congenital heart disease was calculated according to the 10% of patient blood volume. The total blood volume was determined in a patient based on gender, height and weight[12], which was associated with age factor. Since age factor influenced the effect of Voluven infusion for volume expansion and hypovolemia prevention in pediatric patients (Figure 2), we would understand if different infusion volumes have different impacts on Voluven administration in pediatric patients. According to different infusion volumes of Voluven administration, two groups (i.e. low and high infusion) of pediatric patients were divided. Our analysis discovered that the high infusion (250-500 mL per patient) of Voluven administration significantly increased colloid osmotic pressure and central venous pressure, and decreased hemoglobin in the elder child

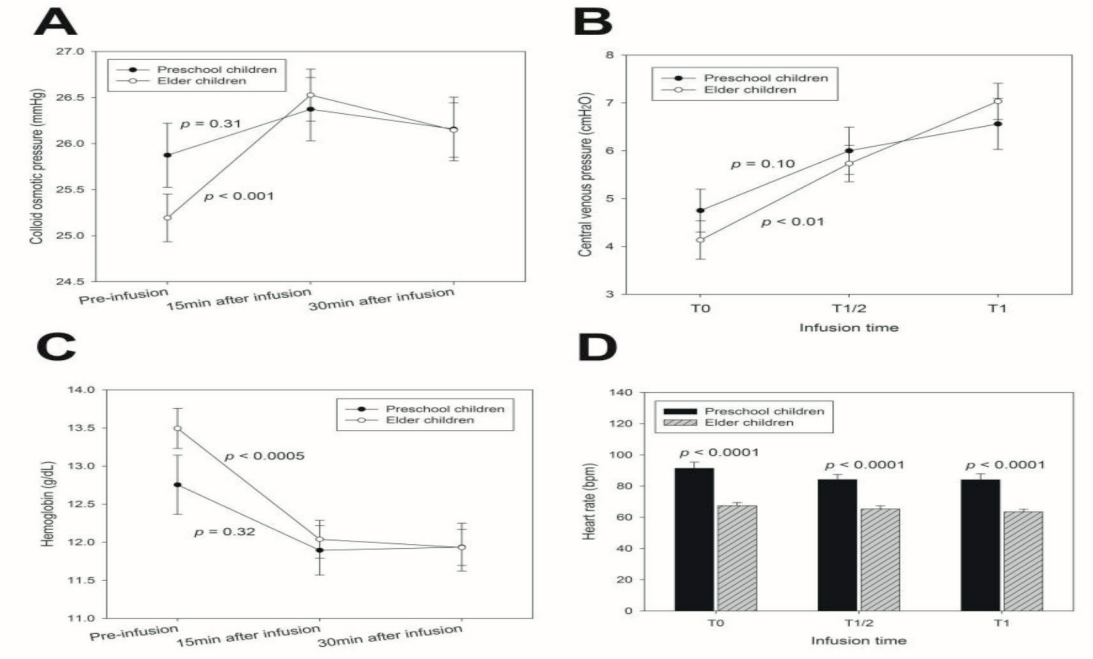


Figure 2. Changes of circulatory parameters in response to Voluven infusion in preschool child patients with congenital heart disease. Pediatric patients with congenital heart disease were divided into two groups, the preschool children (<6 years old) and elder children (>6 years old). Voluven was intravenously administrated in the patients. Colloid osmotic pressure ***(A)*** and hemoglobin ***(C)*** were measured prior to the Voluven infusion, and at 15 min and 30 min after the finish of Voluven infusion. Central venous pressure ***(B)*** and heart rate ***(D)*** were monitored prior to the Voluven infusion (T0), the infusion of half volume of Voluven (T1/2), and the finish of Voluven infusion (T1).

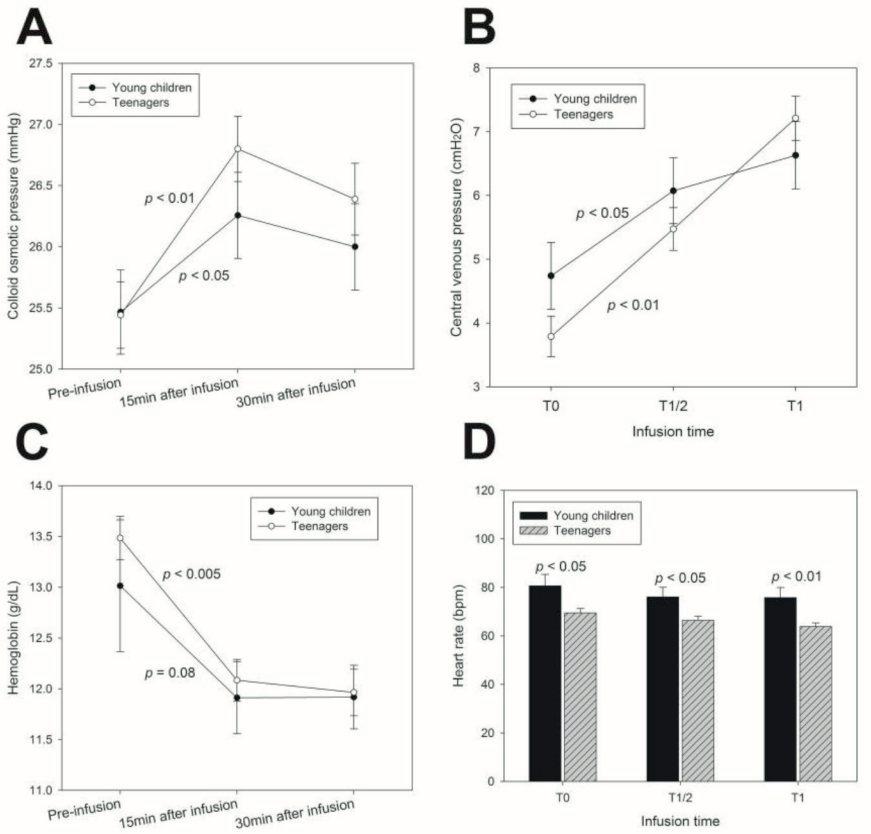


Figure 3. Changes of circulatory parameters in response to Voluven infusion in teenage patients with congenital heart disease. Pediatric patients with congenital heart disease were divided into two groups, the teenagers (>12 years old) and young children (<12 years old). Voluven was intravenously administrated in the patients. Colloid osmotic pressure ***(A)*** and hemoglobin ***(C)*** were measured prior to the Voluven infusion, and at 15 min and 30 min after the finish of Voluven infusion. Central venous pressure ***(B)*** and heart rate ***(D)*** were monitored prior to the Voluven infusion (T0), the infusion of half volume of Voluven (T1/2), and the finish of Voluven infusion (T1).

patients. However, the low infusion (100-240 mL per patient) of Voluven administration did not significantly affect colloid osmotic pressure, central venous pressure, hemoglobin and heart rate in the young child patients (Figure 4). The results suggested that infusion volume influenced the effect of Voluven administration for volume expansion and hypovolemia prevention in pediatric patients, which was consistent with the effect of age factor on Voluven administration (Figure 2). Consistent with the similar responses to Voluven administration between the preschool child patients (Figure 2) and low infusion group of pediatric patients (Figure 4), the low infusion group of pediatric patients had higher levels of airway pressure, peak inspiratory pressure and positive end-expiratory pressure, but lower levels of vascular compliance (Additional Figure 3), which had the same physiological features as the preschool child patients (Additional Figure 1). The results indicated that young child patients (including both preschool child patients and low infusion group of pediatric patients) might have unique physiological features, which may be responsible for the effect of Voluven infusion for volume expansion and hypovolemia prevention in pediatric patients.

Effect of Gender on Voluven Infusion

It has been reported that there were some differences of physiological characteristics including cardiac electrophysiologic properties between males and females[13,14]. There were also anatomical and physiological differences between genders in children[15]. Our analysis showed that female child patients had significantly lower levels of hemoglobin ($p<0.05$, Figure 5C) and high levels of mean arterial pressure ($p<0.0001$, Figure 5D) than male child patients. In response to Voluven infusion, the female child patients only had significantly increased levels of colloid osmotic pressure (Figure

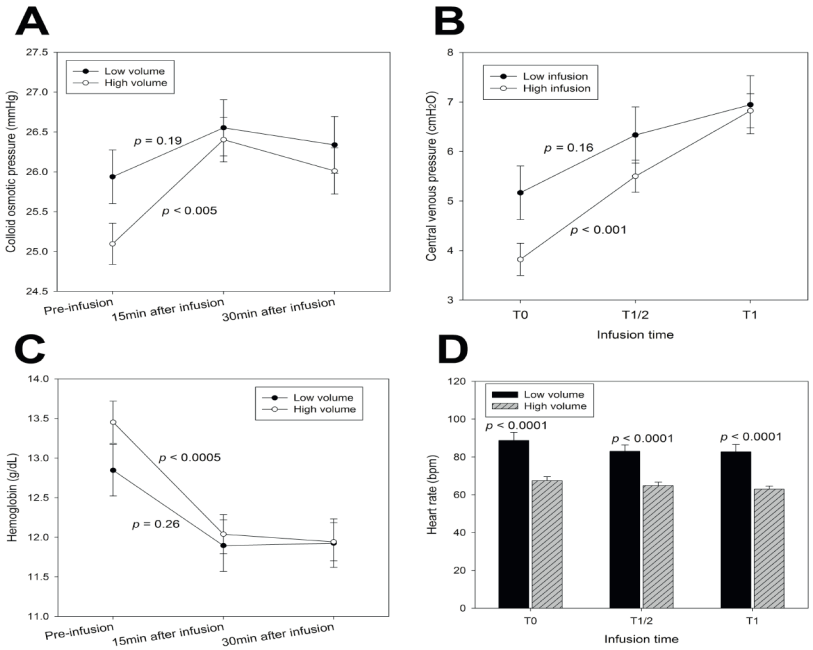


Figure 4. Changes of circulatory parameters in response to low volume of Voluven infusion in pediatric patients with congenital heart disease. Pediatric patients with congenital heart disease were divided into two groups, the patients who received the low volume (100-240 mL per patient) of Voluven administration and those who received the high volume (250-500 mL per patient) of Voluven administration. Voluven was intravenously administrated in the patients. Colloid osmotic pressure ***(A)*** and hemoglobin ***(C)*** were measured prior to the Voluven infusion, and at 15 min and 30 min after the finish of Voluven infusion. Central venous pressure ***(B)*** and heart rate ***(D)*** were monitored prior to the Voluven infusion (T0), the infusion of half volume of Voluven (T1/2), and the finish of Voluven infusion (T1).

5A), while the male child patients had significantly increased levels of colloid osmotic pressure (Figure 5A) and central venous pressure (Figure 5B), but decreased levels of hemoglobin (Figure 5C). The results suggested that gender differences influenced the effect of Voluven infusion for volume expansion and hypovolemia prevention in pediatric patients with congenital heart disease.

Effect of Congenital Heart Disease on Voluven Infusion

Congenital heart disease or congenital heart defect usually includes ASD and VSD[16]. A recent study showed that there were not significant differences between the groups of ASD and VSD in pediatric patients[17]. Our analysis also indicated that there were not any significant differences in circulatory and respiratory parameters including colloid osmotic pressure, central venous pressure, hemoglobin and heart rate between the pediatric patients with ASD and those with VSD before Voluven infusion (Figure 6). In response to Voluven infusion, however, the patients with ASD only had significantly increased levels of colloid osmotic pressure (Figure 6A), while those with VSD had significantly increased levels of colloid osmotic pressure (Figure 6A) and central venous pressure (Figure 6B), but decreased levels of hemoglobin (Figure 6C). The results showed that different congenital heart defects influenced the effect of Voluven infusion for volume expansion and hypovolemia prevention in pediatric patients with congenital heart disease.

Discussion

It has been reported that Voluven (Hydroxyethyl starch 130/0.4) has similar effects on volume expansion and hemodynamics as other available products such as albumin[18]. Also, the Voluven molecule is smaller than those of other available hydroxyethyl starch products, which is believed to be associated with fewer effects on coagulation and may be an acceptable alternative to albumin for volume expansion[3]. Thus, Voluven has been broadly used in clinical settings for volume expansion, hypovolemia prevention and acute normo-

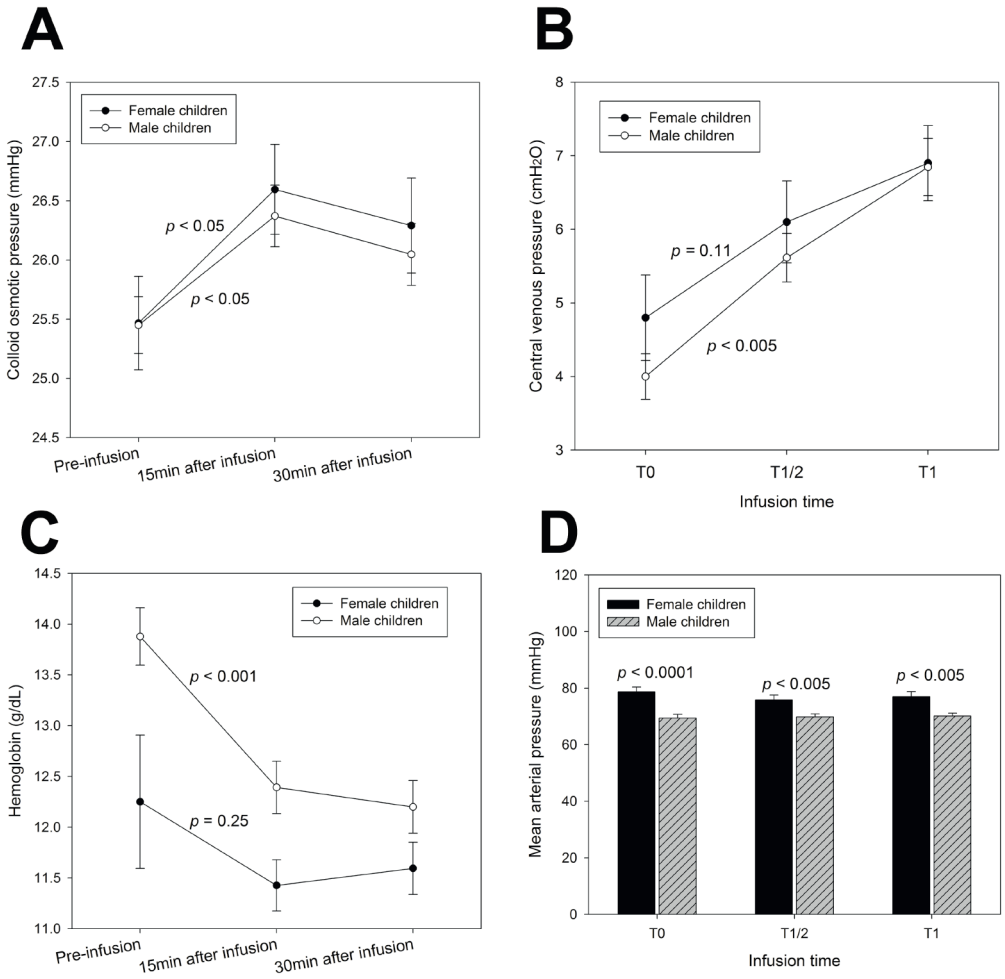


Figure 5. Comparison of changes of circulatory parameters in response to Voluven infusion between female and male pediatric patients with congenital heart disease. Pediatric patients with congenital heart disease were divided into two groups, the female children and male children. Voluven was intravenously administrated in the patients. Colloid osmotic pressure ***(A)*** and hemoglobin ***(C)*** were measured prior to the Voluven infusion, and at 15 min and 30 min after the finish of Voluven infusion. Central venous pressure ***(B)*** and heart rate ***(D)*** were monitored prior to the Voluven infusion (T0), the infusion of half volume of Voluven (T1/2), and the finish of Voluven infusion (T1).

volemic hemodilution[3-5,19]. Multicenter trials have indicated that there were harmful effects of Voluven on patient survival and renal function[20,21]. There are currently limited publications available on the application and safety of Voluven for volume expansion and hypovolemia prevention in pediatric patients with congenital heart disease[8,18,22]. Our studies demonstrated that Voluven could be used for blood volume expansion in the pediatric patients, who required open-surgery repair of heart defects (Figure 1). Our further analysis discovered that the intravenous administration of Voluven did not significantly affect colloid osmotic pressure, central venous pressure, hemoglobin and heart rate in the preschool children (< 6 years old). Consistently, the low infusion (100-240 mL per patient) of Voluven administration did not significantly affect colloid osmotic pressure, central venous pressure, hemoglobin and heart rate in the young child patients (Figure 4). The results suggested that the young pediatric patients (<6 years) did not respond to Voluven infusion as the elder pediatric patients did, thus Voluven may not be used for blood volume expansion and hypovolemia prevention in young pediatric patients with congenital heart disease. As mentioned previously, Voluven molecule is smaller than those of other available hydroxyethyl starch products[3]. Besides, the endothelial glycocalyx layer appears to act as a competent barrier against passage of

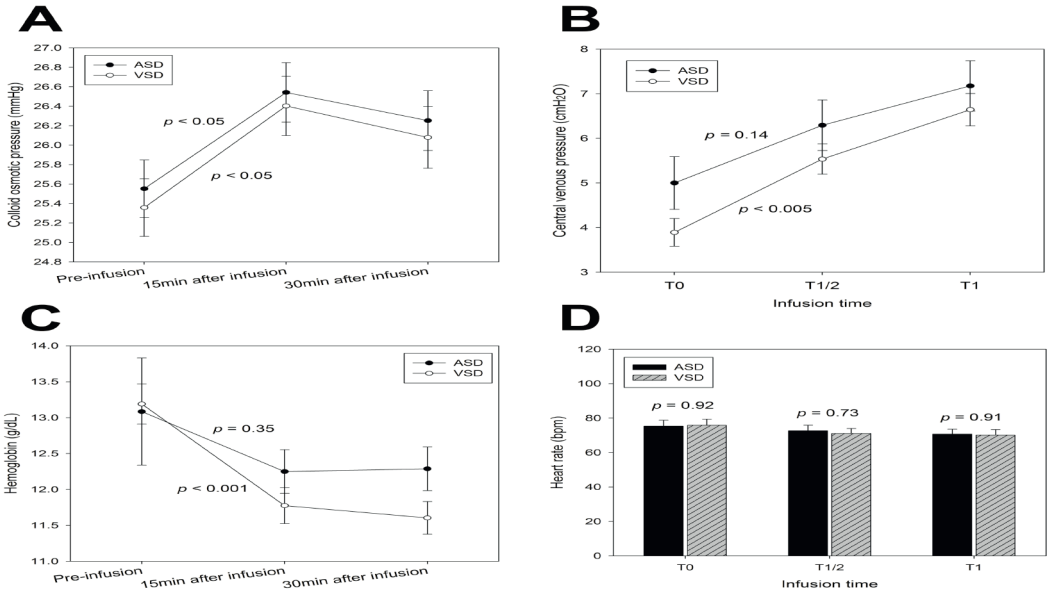
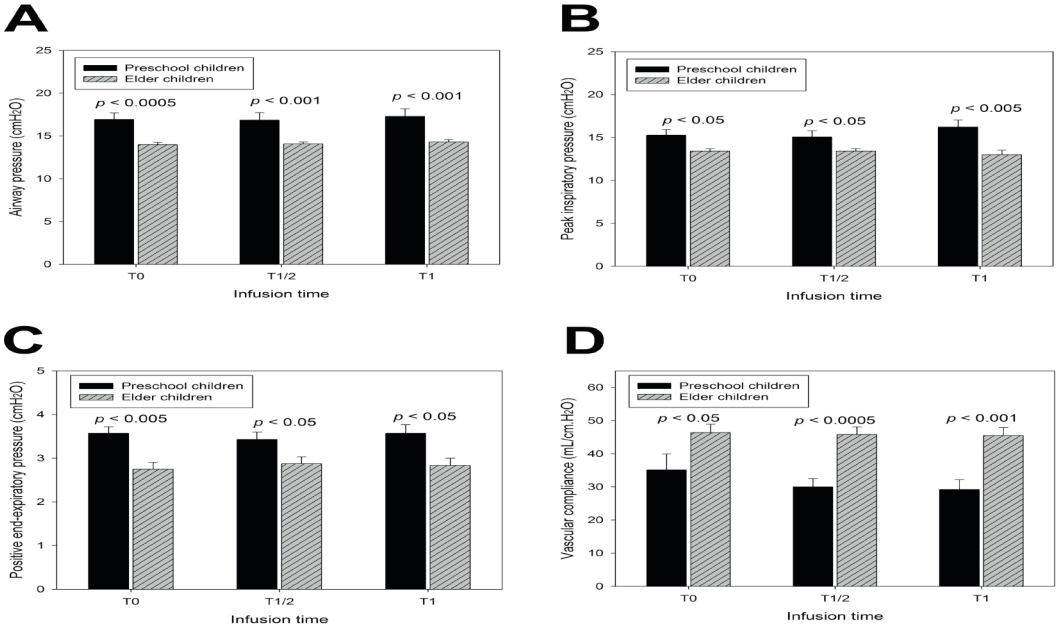
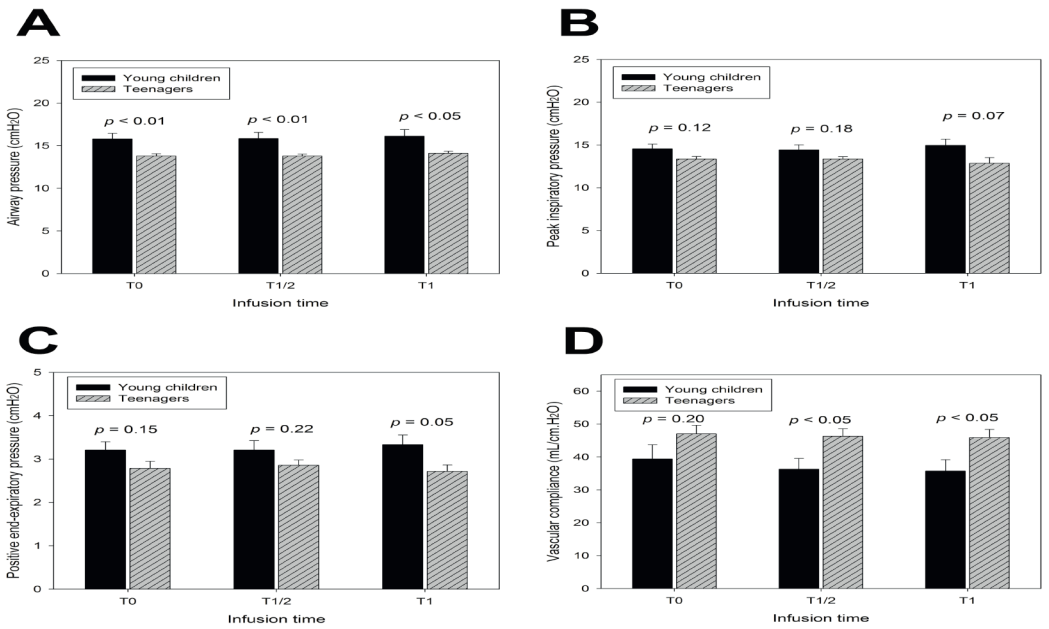


Figure 6. Comparison of changes of circulatory parameters in response to Voluven infusion between pediatric patients with atrial septal defect (ASD) and those with ventricular septal defect (VSD). Pediatric patients with congenital heart disease were divided into two groups, the patients with ASD and those with VSD. Voluven was intravenously administrated in the patients. Colloid osmotic pressure ***(A)*** and hemoglobin ***(C)*** were measured prior to the Voluven infusion, and at 15 min and 30 min after the finish of Voluven infusion. Central venous pressure ***(B)*** and heart rate ***(D)*** were monitored prior to the Voluven infusion (T0), the infusion of half volume of Voluven (T1/2), and the finish of Voluven infusion (T1).

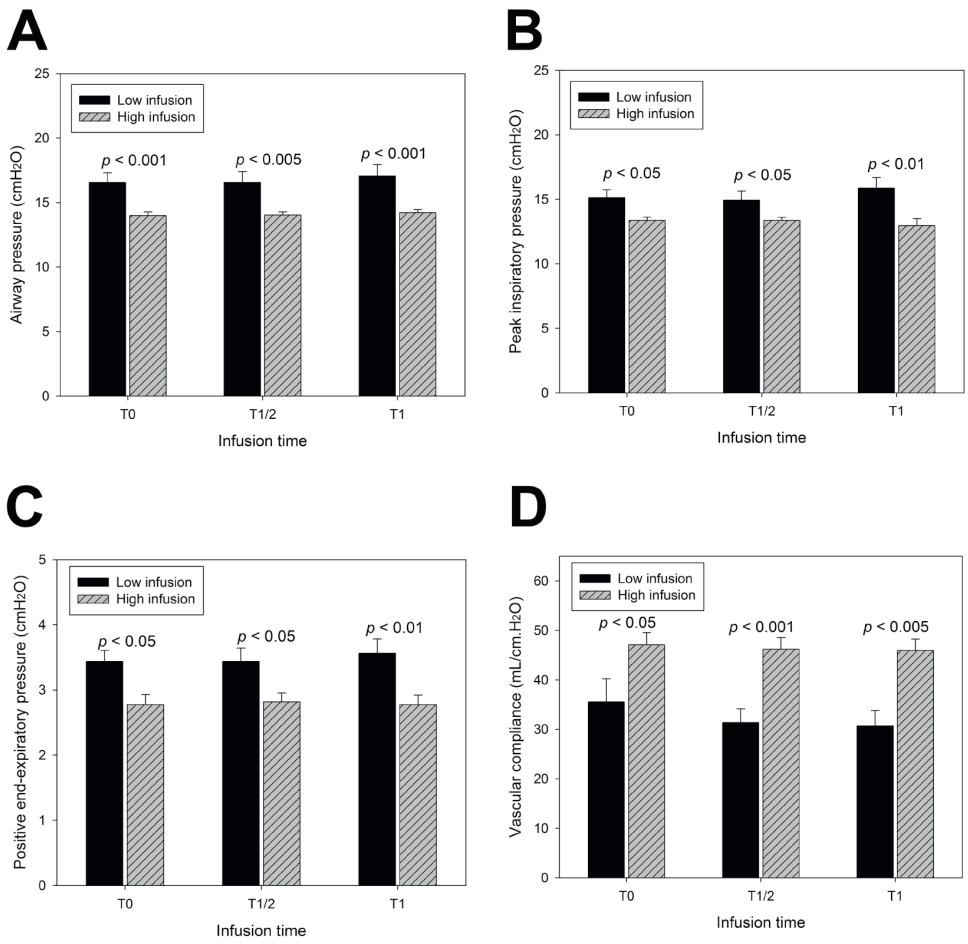
water and colloids such as 6% hydroxyethyl starch[23,24]. It has been reported that the severe degradation of endothelial glycocalyx was detected in infants undergoing cardiac surgical procedures[25]. Thus, young children may not have the well-developed endothelial glycocalyx layer. Voluven may leak through the endothelial glycocalyx layer in the young patients after intravenous infusion. Furthermore, the pediatric patients recruited in this study had normal renal functions and Voluven was not detected in the urine samples from the patients after intravenous infusion (data not shown), suggesting that Voluven did not evacuate through the kidney in the pediatric patients. Also, our measurements showed that the serum concentrations of sodium ion and chloride ion were 140±6 mmol/L and 106±9 mmol/L prior to infusion, 139±7 mmol/L and 105±8 mmol/L at 15 min after the finish of Voluven infusion, and at 30 min after the finish of Voluven infusion, respectively, suggesting that Voluven infusion did not affect the serum levels of Na^+ and Cl^- and there might be a normal renal function in the pediatric patients. The other factors may also contribute to the effect of Voluven infusion for volume expansion and hypovolemia prevention in the young pediatric patients (Additional Figures 1 and 3). However, the exact mechanisms, which determine the effect of Voluven infusion for volume expansion in pediatric patients, are not known thus far. In response to Voluven infusion, the female child patients had significantly increased levels of colloid osmotic pressure (Figure 5A), while the preschool child patients did not have significantly changes in the levels of colloid osmotic pressure (Figure 2A). The results suggested that there were gender differences in response to Voluven infusion in the pediatric patients, which was different from the age factor. Increased levels of colloid osmotic pressure after Voluven infusion suggested that Voluven did not leak out of the capillaries in the female pediatric patients; however, the other circulatory parameters did not change significantly (Figure 5). It has been documented that sex hormones play an important role in the regulation of vascular functions[26]. Sex hormone affected vascular permeability, for instance, estrogen decreased vascular permeability but progesterone augmented vascular permeability[27]. Sex hormones may be responsible for the different responses to Voluven administration in the female pediatric patients. Therefore, sex differences need to be



Additional Figure 1. Comparison of changes of respiratory and circulatory parameters in response to Voluven infusion between the preschool childre n and elder children in pediatric patients with congenital heart disease. Pediatric patients with congenital heart disease were divided into two groups, the preschool children (<6 years old) and elder children (>6 years old). Voluven was intravenously administrated in the patients. Airway pressure ***(A)***, peak inspiratory pressure ***(B)***, positive end-expiratory pressure ***(C)*** and vascular compliance ***(D)*** were measured prior to the Voluven infusion (T0), the infusion of half volume of Voluven (T1/2), and the finish of Voluven infusion (T1).



Additional Figure 2. Comparison of changes of respiratory and circulatory parameters in response to Voluven infusion between the teenagers and young children in pediatric patients with congenital heart disease. Pediatric patients with congenital heart disease were divided into two groups, the teenagers (>12 years old) and young children (<12 years old). Voluven was intravenously administrated in the patients. Airway pressure ***(A)***, peak inspiratory pressure ***(B)***, positive end-expiratory pressure ***(C)*** and vascular compliance ***(D)*** were measured prior to the Voluven infusion (T0), the infusion of half volume of Voluven (T1/2), and the finish of Voluven infusion (T1).



Additional Figure 3. Comparison of changes of respiratory and circulatory parameters in response to Voluven infusion between the patients with low infusion of Voluven and those with high infusion in pediatric patients with congenital heart disease. Pediatric patients with congenital heart disease were divided into two groups, the patients who received the low volume (100-240 mL per patient) of Voluven administration and those who received the high volume (250-500 mL per patient) of Voluven administration. Voluven was intravenously administrated in the patients. Airway pressure (**A**), peak inspiratory pressure (**B**), positive end-expiratory pressure (**C**) and vascular compliance (**D**) were measured prior to the Voluven infusion (T0), the infusion of half volume of Voluven (T1/2), and the finish of Voluven infusion (T1).

considered in the intravenous infusion of Voluven for blood volume expansion and hypovolemia prevention in pediatric patients with congenital heart disease. It was surprising to find out that the patients with ASD only had significantly increased levels of colloid osmotic pressure in response to Voluven infusion (Figure 6), which were different from the patients with VSD (Figure 6), but similar to the female pediatric patients (Figure 5). There were differences of neurodevelopmental outcomes including visuospatial processing, language, attention, and social perception between pediatric patients with ASD and those with VSD after surgery for acyanotic congenital heart disease[28]. There were different effects of respiratory vagal activity on heart rate variability between the patients with ASD and those with VSD[29]. It was assumed that the patients with ASD might have unknown unique features, which were responsible for specific responses to Voluven infusion in the pediatric patients. Thus, it should be cautious when Voluven is used for volume expansion and hypovolemia prevention in pediatric patients with atrial septal defect.

Conclusions

We demonstrated that Voluven could be used in pediatric patients with congenital heart disea-

se, but not in the preschool child patients (< 6 years old). Furthermore, special attention should be paid to the intravenous administration of Voluven for volume expansion and hypovolemia prevention in female pediatric patients and child patients with atrial septal defect.

Trial registration

This study was registered in the Chinese Clinical Trial Registry (the clinical trial registration No. ChiCTR-IPR-15006963).

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Conflict of interest

The authors declare no conflicts of interest.

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