Effects of Positive End-Expiratory Pressure Ventilation and Extracorporeal Ultrafiltration Method in Patients with Refractory Heart Failure

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We studied the effects of positive end-expiratory pressure (PEEP) ventilation in ten patients with acute myocardial infarction (nine in Killip class III, one in Killip class IV; pulmonary capillary wedge pressure > 24 mmHg) and of extracorporeal ultrafiltration method (ECUM) in seven patients with refractory heart failure due to acute myocardial infarction and others. (1) Application of PEEP resulted in significant increases in PaO_2 and SaO_2 and decrease in PaCO_2 . Significant reduction in mean pulmonary arterial and pulmonary capillary wedge pressures and heart rate was observed, while stroke work index increased significantly. There was a significant correlation between changes in stroke work index and PaO_2 after the application of PEEP. (2) The use of ECUM removed fluid of 1416 ± 662 ml (680–2800 ml) with the ultrafiltration flux rate being 478 ± 223 ml/hour. Significant decreases in mean pulmonary arterial, pulmonary capillary wedge and central venous pressures were observed, while PaO_2 increased significantly. BUN and serum creatinine levels increased significantly, and total protein and serum albumin tended to increase. There was a significant correlation between fluid removed and change in PaO_2 after the use of ECUM.

Thus, PEEP and ECUM are beneficial for patients with refractory heart failure. The mechanism(s) are: (1) reduction in preload due to an increased intrathoracic pressure and a decreased systemic venous return with PEEP, or due to removal of excess fluid with ECUM, and (2) improvement of the oxygenation of the blood.

TREATMENT of refractory heart failure and cardiogenic shock due to acute myocardial infarction with digitalis, diuretics, vasodilators and inotropic agents is often unsatisfactory, necessitating the use of mechanical circulatory support such as intraaortic balloon pumping (IABP). Intermittent positive pressure breathing (IPPB) and positive end-expiratory pressure (PEEP) have been used in patients with severe pulmonary congestion or pulmonary edema

to improve the oxygenation of the blood^{1,2} as has the extracorporeal ultrafiltration method (ECUM) to remove excess sodium and water.

The purpose of this investigation was to examine the hemodynamic and biochemical effects as well as the effects on arterial blood gas of PEEP and ECUM in patients with refractory heart failure due to acute myocardial infarction.

METHODS

To evaluate the effects of PEEP we studied ten patients (seven men and three women) with a mean age of 62 years (range 51 to 78) who had

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TABLE I CLINICAL DATA

Case No.	Age (yr)	Sex	Site of infarct	Killip class	Blood gas tensions			During artificial respiration					Prognosis
					PaO ₂ (mmHg)	PaCO ₂ (mmHg)		PaO ₂ (mmHg)	PaCO ₂ (mmHg)	FiO ₂	PEEP (cmH ₂ O)	Days of PEEP	
1	54	M	AL	III	53.9	37.0		109.9	35.7	0.35	15	12	died
2	52	M	AL	III	53.2	35.9		221.0	37.3	1.0	6	43	died
3	56	F	AL	III	64.8	66.6		82.9	32.1	0.5	5	45	died
4	51	M	AL	III	85.5	25.0		135.6	27.1	0.6	15	9	died
5	78	F	A	III	74.2	38.8		84.6	35.4	0.4	10	16	died
6	58	M	AL	IV	60.7	40.8		125.9	28.3	0.5	5	7	died
7	75	M	A	III	46.6	40.6		107.1	22.1	1.0	5	13	survived
8	59	M	A	III	67.8	81.6		284.4	43.7	1.0	6	3	survived
9	62	M	AL	III	56.6	42.3		114.0	39.3	0.85	8	2.5	survived
10	77	F	I	III	53.5	36.1		157.5	34.5	1.0	10	0.4	survived
	62.2 ± 10.5				63.4 ± 12.2	44.5 ± 16.7		151.3 ± 61.5	33.6 ± 6.3	0.72 ± 0.27	8.5 ± 3.9	15.1 ± 16.0	

AL = anterolateral infarction; A = anterior infarction; I = inferior infarction; PEEP = positive end-expiratory pressure

clinical evidence of persistent severe congestive heart failure due to acute myocardial infarction and hypoxemia despite the inhalation of oxygen (Table I). Nine patients were in Killip class III and one in Killip class IV. All patients had pulmonary capillary wedge pressure greater than 24 mmHg. Each patient was put on a volume-limited respirator (Bennet MA-1B, Servo Ventilator) with a mean of 8.5 cmH₂O (range 5 to 15 cmH₂O) of PEEP and 0.35 to 1.0 of FiO₂.

To evaluate the effects of ECUM we studied seven patients (48 to 80 years, six men and one woman) with severe congestive heart failure (Table II). Congestive heart failure was due to acute myocardial infarction in four patients, two of them having the added complication of papillary muscle dysfunction; combined valvular heart disease, hypertensive heart disease and beriberi heart disease were each experienced by one patient. IABP was performed in two patients, artificial respiration in five and conventional therapy with digitalis, diuretics, vasodilators and inotropic agents in all patients. Five patients were complicated with acute or chronic renal failure.

The ultrafiltration cell C-DAK™ 3500 dialyzer was used. Access to blood stream was obtained by a 7F catheter placed in the femoral vein with venous return through 16-gauge needle placed in the antecubital vein. Blood circulation through the ultrafiltration cell was maintained by a roller blood pump (Sars S₁₀K) and the transmembrane pressure was 150 to 250 mmHg.

Hemodynamic parameters were obtained with a Swan-Ganz catheter and arterial blood samples were analysed for pH, pO₂ and pCO₂ (Radiometer, Copenhagen ABL-II) before and during the application of PEEP or ECUM.

RESULTS

1. Effects of PEEP application

Hemodynamic and laboratory data are summarized in Fig. 1 and Table III. Application of PEEP resulted in significant increases in PaO₂ from 63.4 ± 12.2 to 151.1 ± 61.5 mmHg ($p < 0.01$) and SaO₂ from 83.4 ± 15.5 to 97.9 ± 2.5% ($p < 0.05$), while PaCO₂ decreased significantly from 44.5 ± 16.7 to 33.6 ± 6.3 mmHg ($p < 0.05$). Significant reduction in mean pulmonary arterial pressure from 42.6 ± 9.9 to 30.7 ± 8.6 mmHg ($p < 0.01$), pulmonary capillary wedge pressure from 31.8 ± 8.1 to 23.8 ± 6.7 mmHg ($p < 0.01$), and heart rate from 105 ± 21 to 96 ± 20

TABLE II CLINICAL DATA

Case No.	Age (yr)	Sex	Diagnosis	Treatment	Prognosis
1	53	M	AMI (inferior), papillary muscle dysfunction, complete AV block	Artificial respiration (FiO ₂ 0.5), IABP, β -MD, furosemide, dopamine, artificial pacemaker	survived
2	59	M	AMI (pure posterior), ventricular tachycardia, DM	β -MD, ISDN, furosemide, spironolactone	survived
3	49	M	AMI (anterolateral), cerebral hemorrhage, acute renal failure, DM	IABP, digoxin, furosemide, spironolactone, dopamine, norepinephrine	died
4	74	M	AMI (inferior), papillary muscle dysfunction, cardiogenic shock, chronic renal failure, pneumonia	Artificial respiration (FiO ₂ 0.5), digoxin, furosemide, spironolactone, dobutamine, nitroglycerine (iv)	died
5	60	F	Combined valvular disease, sinus bradycardia, sepsis, DIC, chronic renal failure, pneumonia	Artificial respiration (FiO ₂ 0.5), hydralazine, furosemide, spironolactone, dopamine	died
6	80	M	Hypertensive heart disease, complete AV block, chronic renal failure	Artificial respiration (FiO ₂ 0.5), digoxin, furosemide, artificial pacemaker	died
7	48	M	Beriberi heart disease, acute renal failure	Artificial pacemaker (FiO ₂ 0.5), dopamine, furosemide	survived

AMI = acute myocardial infarction; DM = diabetes mellitus; IABP = intraaortic balloon pumping; β -MD = β -methyldigoxin, ISDN = isosorbide dinitrate, AV = atrioventricular

TABLE III CHANGES IN PH AND BLOOD GAS TENSIONS, AND HEMODYNAMICS AFTER THE APPLICATION OF POSITIVE END-EXPIRATORY PRESSURE

	n	Before	After	p
Arterial oxygen tension (mmHg)	10	63.4 $\pm$ 12.2	151.1 $\pm$ 61.5	p < 0.01
Arterial carbon dioxide tension (mmHg)	10	44.5 $\pm$ 16.7	33.6 $\pm$ 6.3	p < 0.05
Arterial pH	10	7.35 $\pm$ 0.21	7.496 $\pm$ 0.09	p < 0.05
Arterial oxygen saturation (%)	10	83.4 $\pm$ 15.5	97.9 $\pm$ 2.5	p < 0.05
Hemoglobin (g/dl)	10	11.1 $\pm$ 2.5	11.4 $\pm$ 2.6	NS
O ₂ transport	10	49.3 $\pm$ 25.8	57.5 $\pm$ 30	NS
Heart rate (beats/min)	10	105 $\pm$ 21	96 $\pm$ 20	p < 0.05
Mean blood pressure (mmHg)	10	88.1 $\pm$ 19.1	85.7 $\pm$ 12.9	NS
Central venous pressure (mmH ₂ O)	10	16.4 $\pm$ 7.0	13.9 $\pm$ 3.7	NS
Mean pulmonary arterial pressure (mmHg)	10	42.6 $\pm$ 9.9	30.7 $\pm$ 8.6	p < 0.01
Pulmonary capillary wedge pressure (mmHg)	10	31.8 $\pm$ 8.1	23.8 $\pm$ 6.7	p < 0.01
Pulmonary vascular resistance (dynes $\cdot$ sec $\cdot$ cm ⁻⁵)	10	211.4 $\pm$ 102.8	158.1 $\pm$ 112.5	NS
Cardiac index (l/min/m ²)	10	2.53 $\pm$ 0.69	2.59 $\pm$ 0.79	NS
Stroke volume index (ml/beat/m ²)	10	25.6 $\pm$ 11.0	28.0 $\pm$ 12.0	NS
Stroke work index (gm $\cdot$ m/beat/m ²)	10	19.1 $\pm$ 8.7	24.4 $\pm$ 14.8	p < 0.05
Total peripheral resistance (dynes $\cdot$ sec $\cdot$ cm ⁻⁵)	10	1652 $\pm$ 492	1627 $\pm$ 571	NS
Transmyocardial pressure gradient (mmHg)	10	42.1 $\pm$ 16.4	46.7 $\pm$ 12.7	NS
Double product	10	12263 $\pm$ 4758	10675 $\pm$ 2398	NS

beats/min, and significant increase in stroke work index from 19.1 $\pm$ 8.7 to 24.4 $\pm$ 14.8 gm $\cdot$ m/beat/m² were observed with PEEP. There

was a tendency to increase in cardiac index, stroke volume index, transmyocardial pressure gradient and O₂ transport, and to decrease in

Fig.1. Hemodynamic changes after the application of positive end-expiratory pressure.

HR = heart rate; BPm = mean systemic arterial pressure; PAPm = mean pulmonary arterial pressure; PCWP = mean pulmonary capillary wedge pressure; CI = cardiac index; SWI = stroke work index; B = before; A = after

mean blood pressure, central venous pressure, pulmonary vascular resistance, total peripheral resistance and double product, but these changes were not significant.

There was a significant correlation between changes in stroke work index and PaO_2 ($r = 0.670$, $p < 0.05$, Fig. 2, left). Change in SaO_2 correlated significantly with change in mean pulmonary arterial pressure ($r = -0.671$, $p < 0.05$, Fig. 2, right). The level of PEEP did not correlate with changes in hemodynamic

parameters.

2. Effects of ECUM application

The application of ECUM removed 1416.4 ± 662.2 ml fluid (range, 680 to 2850 ml) during the course of 3.46 ± 1.7 hours (range, 1.5 to 6 hours) with the ultrafiltration flux rate being 477.5 ± 223.4 ml/hour (8 ml/min).

Changes in hemodynamic and laboratory data during the application of ECUM are shown in Fig. 3 and Table IV. Significant decrease in

Fig.2. The relations between change in stroke work index (ΔSWI) and change in partial arterial oxygen tension (ΔPaO_2) and between change in mean pulmonary arterial pressure (ΔPAm) and change in arterial oxygen saturation (ΔSaO_2)

Fig.3. Changes in hemodynamics, arterial oxygen tension (PaO_2), serum creatinine (Crn), blood urea nitrogen (BUN) and serum electrolytes (Na, K, Cl) after the application of extracorporeal ultrafiltration method.

HR = heart rate; BPm = mean blood pressure; PAPm = mean pulmonary arterial pressure; PCWP = mean pulmonary capillary wedge pressure; CVP = central venous pressure; CI = cardiac index; B = before; A = after

TABLE IV CHANGES IN HEMODYNAMICS, PH AND BLOOD GAS TENSIONS AND BIOCHEMICAL DATA AFTER THE APPLICATION OF EXTRACORPOREAL ULTRAFILTRATION METHOD

	<i>n</i>	<i>Before</i>	<i>After</i>	<i>p</i>
Heart rate (beats/min)	11	92.7 ± 20.7	93.8 ± 21.4	NS
Mean blood pressure (mmHg)	11	86.0 ± 14.4	84.9 ± 19.2	NS
Central venous pressure (cmH ₂ O)	11	15.2 ± 4.8	12.5 ± 4.0	<i>p</i> < 0.05
Mean pulmonary arterial pressure (mmHg)	10	37.1 ± 8.5	31.5 ± 9.2	<i>p</i> < 0.05
Pulmonary capillary wedge pressure (mmHg)	10	27.4 ± 6.8	21.5 ± 8.1	<i>p</i> < 0.05
Pulmonary vascular resistance (dynes·sec·cm ⁻⁵)	10	208.5 ± 102.4	252.1 ± 152.4	NS
Cardiac index (l/min/m ²)	10	2.50 ± 0.52	2.42 ± 0.81	NS
Stroke volume index (ml/beat/m ²)	10	29.3 ± 14.7	28.8 ± 15.7	NS
Stroke work index (gm-m/beat/m ²)	10	26.6 ± 20.8	27.9 ± 21.6	NS
Total peripheral resistance (dynes·sec·cm ⁻⁵)	10	1459 ± 298	1557 ± 385	NS
Transmyocardial pressure gradient (mmHg)	10	30.8 ± 12.4	36.3 ± 14.8	NS
Double product	11	12527 ± 3534	12215 ± 3713	NS
Arterial pH	9	7.44 ± 0.09	7.46 ± 0.06	NS
Arterial oxygen tension (mmHg)	9	100.9 ± 31.0	135.0 ± 46.8	<i>p</i> < 0.05
Arterial carbon dioxide tension (mmHg)	9	34.9 ± 6.6	32.3 ± 3.4	NS
BUN (mg/dl)	10	107.0 ± 70.6	125.7 ± 67.4	<i>p</i> < 0.01
Serum creatinine (mg/dl)	10	5.1 ± 3.1	6.3 ± 4.0	<i>p</i> < 0.05
Serum sodium (mEq/l)	11	139.3 ± 9.9	140.4 ± 9.7	<i>p</i> < 0.05
Serum potassium (mEq/l)	11	4.2 ± 0.9	4.7 ± 0.9	<i>p</i> < 0.05
Serum chloride (mEq/l)	11	97.6 ± 8.4	97.8 ± 8.4	NS
Hemoglobin (g/dl)	10	10.0 ± 2.2	9.87 ± 2.37	NS
Total protein (g/dl)	10	6.16 ± 0.52	6.27 ± 0.62	NS
Serum albumin (g/dl)	10	3.34 ± 0.27	3.43 ± 0.29	NS

mean pulmonary arterial pressure from 37.1 ± 8.5 to 31.5 ± 9.2 mmHg, pulmonary capillary wedge pressure from 27.4 ± 6.8 to 21.5 ± 8.1 mmHg and central venous pressure from 15.2 ± 4.8 to 12.5 ± 4.0 cmH₂O was observed after the application of ECUM. Cardiac index, stroke volume index and mean blood pressure tended to decrease, and transmyocardial pressure gradient tended to increase with ECUM, but they did not reach the required level of significance.

PaO₂ increased significantly from 100.9 ± 31.0 to 135 ± 46.8 mmHg after ECUM in all patients except one (Case 3, Table II) in whom ECUM was performed twice during the application of IABP, and PaO₂ decreased after ECUM. PaCO₂ did not alter significantly. There was a significant increase in BUN level from 107.1 ± 70.6 to 125.7 ± 67.4 mg/dl, and creatinine level from 5.1 ± 3.1 to 6.3 ± 4.0 mg/dl. The serum sodium level increased from 139.3 ± 9.9 to 140.4 ± 9.7 mEq/l and the serum potassium level from

4.2 ± 0.9 to 4.7 ± 0.9 mEq/l, but the serum chloride level did not change significantly. The total protein and the serum albumin tended to increase, but the changes were not significant. There was a significant correlation between fluid removed and change in PaO₂ (*r* = 0.681, *p* < 0.05, Fig. 4).

DISCUSSION

In patients with acute myocardial infarction, the circulation is delicately balanced.³ When regional myocardial dysfunction is limited and the function of the remainder of the left ventricle is normal, compensatory mechanisms will sustain overall left ventricular function. If the infarct is of significant size, pump failure develops. Hypoxemia is a frequent consequence, with its severity, in general, proportional to that of left ventricular failure. Intrapulmonary shunt of blood has been noted in patients in whom left

Fig.4. The relationship between the fluid removed and change in partial arterial oxygen tension (ΔPaO_2) after the application of extracorporeal ultrafiltration method.

ventricular failure complicates acute myocardial infarction. Excessive secretion of catecholamines and aldosterone leads to retention of sodium and water in the body and overhydration, necessitating the use of ECUM⁴⁻⁸

1. PEEP

Although in 1938 Barach et al. used positive pressure respiration for the treatment of acute pulmonary edema,⁹ physicians have been reluctant to use PEEP in the management of patients with compromised cardiac function because of cardiac output reduction due to a decrease in venous return and restriction of ventricular filling by positive pressure. PEEP ventilation has been reported to improve arterial oxygenation and is used in acute respiratory failure.^{1,10}

Several investigators have reported a reduction in cardiac output with the application of PEEP^{9,11-15} although this effect is not consistent.^{1,16-18} Morgan et al. reported that cardiac output and stroke volume decreased with increasing airway pressure in lightly anesthetized dogs.¹¹ Oxygen transport which is the product of cardiac index and arterial oxygen content has been reported to decrease with the use of PEEP owing to a significant reduction in cardiac index despite the increase of arterial oxygen content.^{14,19} Several mechanisms have been reported to explain this observation: (i) a decrease in systemic venous return; (ii) decreased right ventricular function;¹⁵ (iii) decreased left ventricular function;^{20,21} (iv) neurally or humorally mediated cardiac output reduction,^{11,15} and

Fig.5. Mechanisms of beneficial effects of extracorporeal ultrafiltration method (ECUM) in patients with refractory heart failure.

CVP = central venous pressure; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; COP = colloid osmotic pressure; PaO₂ = partial arterial oxygen tension; TMG = transmyocardial pressure gradient

(v) cardiac output reduction secondary to endocardial blood supply impairment.¹⁵ On the other hand, Kumar et al. reported an increase in cardiac output in 8 patients with acute respiratory failure.¹ Colgan et al. reported that the use of PEEP in patients following heart-valve surgery increased cardiac index in patients with a cardiac index below 2.5 l/min/m², while a reduction in cardiac index was observed in patients with a cardiac index greater than 2.5 l/min/m².¹⁶ Grace et al. evaluated the effects of PEEP on cardiac performance in patients with left ventricular dysfunction and found that cardiac output increased in one of four patients with pulmonary capillary wedge pressure less than 12 mmHg, in 4 of 6 patients with pulmonary capillary wedge pressure of 14 to 18 mmHg and in 12 of 13 patients with pulmonary capillary wedge pressure greater than 18 mmHg.¹⁸ Greenbaum²⁰ mentioned that the use of PEEP improved cardiac output in the majority of patients with myocardial infarction when pulmonary capillary wedge pressure was greater than 18 mmHg.

The present investigation showed that the use of PEEP improved the oxygenation of the blood and decreased pulmonary capillary wedge pressure in patients with severe pump failure due to

acute myocardial infarction. Increase in cardiac output was observed in seven of 10 patients while cardiac output decreased in three patients. The application of PEEP increased stroke work index and improved cardiac performance with a decrease in pulmonary capillary wedge pressure in patients with highly elevated pulmonary capillary wedge pressure, while in patients with slightly elevated pulmonary capillary wedge pressure or relatively increased stroke work index, the use of PEEP decreased stroke work index with a decrease in pulmonary capillary wedge pressure.

Thus, we concluded that this application of PEEP is beneficial for patients with severe pump failure due to acute myocardial infarction. The mechanism(s) may relate to (1) reduction in preload due to an increase in intrathoracic pressure and a decrease in systemic venous return; and (2) improvement of the oxygenation of the blood and of the metabolism of the ischemic myocardium. PEEP must be applied so that oxygen transport to the peripheral tissue is maximal ("best PEEP").¹⁷

2. ECUM

ECUM, developed by Kobayashi et al. in 1972, is a method of controlling body fluids in patients suffering from overhydration,⁴ removing excess sodium and water by ultrafiltration. ECUM has been reported to be effective in patients with chronic renal failure due to chronic nephritis,^{4,8,22-25} nephrotic syndrome,^{4,23,26} liver cirrhosis,²⁶ heart failure due to various causes^{5,6,8,26} or cardiogenic shock.⁷

Poggliusch et al.⁸ reported that the use of ECUM in patients with severe refractory edema decreased plasma volume from 3560 to 2524 ml, central venous pressure from 20.4 to 5.2 cmH₂O, and mean blood pressure from 110 to 101 mmHg, and increased the hematocrit value from 36 to 43 percent. Paganini et al.²⁵ mentioned that the application of ECUM caused significant reductions in extracellular fluid, from 19.5 to 17.9 liters, reduced plasma volume from 4.2 to 3.7 liters and reduced body weight from 83.0 to 81.0 kg, while cardiac output, heart rate, blood pressure, and total systemic vascular resistance did not alter significantly. The present investigation showed that in patients with refractory heart failure, the use of ECUM significantly decreased mean pulmonary arterial, pulmonary capillary wedge and central venous pressures, while heart rate, blood pressure, and cardiac

index did not change and transmyocardial pressure gradient tended to increase. PaO₂ increased significantly with the use of ECUM, the increment being correlated with the volume of fluid removed. Thus, in patients with refractory heart failure and overhydration, the application of ECUM removed excess water and improved pulmonary congestion and oxygenation of the blood.

The mechanism(s) may relate to reduction in preload and increase in plasma osmolarity due to removal of excess fluid, which decreases pulmonary congestion and improves oxygenation of the blood, resulting in the improvement of cardiac performance (Fig. 5).

Maeda et al.⁵ mentioned that the use of ECUM for the treatment of refractory heart failure was indicated (1) in patients whose renal response to diuretics was impaired due to dilutional hyponatremia, and (2) in patients in whom diuretics are not effective due to renal failure. Nishizaki et al.⁶ reported that ultrafiltration was effective in a patient with refractory heart failure due to congestive cardiomyopathy complicated with diabetes mellitus, and that the use of ECUM was indicated in patients with heart failure (1) when refractory to the conventional treatment with digitalis, diuretics and vasodilators, and (2) when left ventricular filling pressure was highly elevated (≥ 25 mmHg).⁶ In the present study, all patients had elevated pulmonary capillary wedge pressure greater than 18 mmHg despite the use of digitalis, diuretics, vasodilators, catecholamine, PEEP, or IABP, and had generalized edema or pretibial edema. Four of seven patients were complicated with acute or chronic renal failure.

In this study, the extracorporeal circuit was: vein $\rightarrow$ a roller pump $\rightarrow$ a dializer $\rightarrow$ vein. Kramer et al.²⁴ described that fluid withdrawal in overhydrated patients resistant to diuretics was obtained by means of a capillary hemofilter, using the arteriovenous pressure gradient for blood perfusion at a rate of 100 ml/min.

Kobayashi et al.⁴ reported that the use of ECUM did not increase the levels of serum creatinine, BUN, serum uric acid and serum electrolytes (Na, Cl, P, Ca) after fluid removal of 420 to 2000 ml (5.6 to 28.3 ml/min). Asaba et al. reported increases in serum protein by 1.69 g/dl, serum sodium by 2.7 mmol/l, and hematocrit value by 5.8 percent, while serum creatinine level and serum potassium did not change.²⁶ In our study, the levels of serum

creatinine, BUN, serum sodium and serum potassium increased significantly with the application of ECUM, which was related to the fluid removal.

There were no side effects with ECUM in our study, such as chills, fever, headache, orthostatic hypotension or muscle cramp^{4,22}

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