Yonsei Medical Journal
Vol. 39, No. 3, pp. 189~195, 1998

☐ Original Article ☐

Does Low Dose Dopamine Attenuate the Decrease of Renal Function in the Treatment of Patients under Controlled Mechanical Ventilation with Positive End Expiratory Pressure?

Yong Jeong Kim[1], Cheung Soo Shin[2], Jung Lyul Kim[2], Jin Soo Kim[2], Hoon Sang Chi[1], and Eui Woon Lee[2]

Controlled mechanical ventilation(CMV) with positive end expiratory pressure (PEEP) is often used to improve the pulmonary gas exchange in patients with acute respiratory distress syndrome. However, this ventilatory technique may induce hemodynamic and hormonal changes which may lead to vital organ dysfunction, such as oliguria. Low dose dopamine, acting as a dopaminergic receptor agonist, may improve vital organ perfusions, i. e. renal, mesenteric and coronary perfusions. The purpose of this current study was to evaluate the effects of low dose dopamine on renal function and hemodynamic change during controlled mechanical ventilation with PEEP. The study was performed on 10 patients treated with PEEP in the surgical intensive care unit. Starting with 0 cmH_2O of PEEP and adding 4 cmH_2O of PEEP at 4-hour intervals until it reached 12 cmH_2O of PEEP, dopamine, 2 ug/kg/min, was selectively administered, intravenously during the last two hours of each four hour intervals. Following each procedure, hemodynamic parameters, urine output, creatinine clearance and fractional excretion of sodium were measured. The cardiac index and mean arterial pressure had both decreased, but the mean pulmonary arterial pressure was increased at 12 cmH_2O of PEEP compared with 0 cmH_2O of PEEP in both groups with and without low dose dopamine. The main result of this study was that low dose dopamine attenuated the decrease of the cardiac index, urine output and creatinine clearance induced by mechanical ventilation with PEEP at 12 cmH_2O.

Key Words: PEEP, dopamine, hemodynamics, renal function

Positive end expiratory pressure (PEEP) for adequate ventilation and tissue oxygen tension is frequently employed for the treatment of critically ill patients in intensive care units. Because controlled mechanical ventilation(CMV) with PEEP increases intrathoracic pressure, venous return and cardiac output may decrease (Hevroy and Klow, 1991). Reduction in the cardiac output can affect the renal perfusion, decreasing renal function and urine output.

Renal function is a critical factor for patients in intensive care units. Post-surgical or post trauma patients are frequently required to have mechanical ventilation with PEEP for adequate oxygenation. This may compromise renal function.

Since one of the main causes of this functional disturbance is low renal perfusion, efforts are made to increase the renal perfusion during this kind of therapy. Intravenous volume expansion may prevent or improve acute renal dysfunction in this situation.

Received January 26, 1998
Accepted May 22, 1998
Departments of [1]Surgery and [2]Anesthesiology, Yonsei University College of Medicine, Seoul, Korea
Address reprint request to Dr. C.S. Shin, Department of Anesthesiology, Yongdong Severance Hospital, Yonsei University College of Medicine, Yongdong P.O. Box 1217, Seoul 135-270, Korea

Fluid administration in critically-ill patients, however, can worsen pulmonary function. In such cases, low dose dopamine may be the choice of treatment (Venus *et al.* 1985).

Dopamine is the precursor of norepinephrine and shows various effects depending on the dosage. It acts on dopaminergic receptors and increases the perfusion to renal, mesenteric and coronary arteries at low doses. The increase in renal blood flow increases urine output thereby protecting the renal function (Poinsot *et al.* 1993). However, the effect of low dose dopamine on the protection of renal function has been questioned in some studies (Duke and Bernsten,1990; Szerlip, 1991; Duke *et al.* 1994).

The purpose of the present study was to determine whether low dose dopamine can improve the reduced renal function induced by PEEP.

MATERIALS AND METHODS

The present study was performed on 10 adult patients who received mechanical ventilation with PEEP in the intensive care unit of Yonsei University Yongdong Severance Hospital. The male to female ratio was 1 : 1.5(Table 1). The mean age of the subjects was 53.9 years, ranging from 32 to 77 years. Patients who required mechanical ventilation using PEEP for the maintenance of arterial oxygen tension, and those who showed stable hemodynamic parameters were included in the study. Patients with anemia, pregnancy, uncontrolled ventricular arrhythmia, and renal dysfunction, electrolyte abnormality, or thrombocytopenia ($<75,000/mm^3$), as well as those who required diuretics, vasoconstrictor or vasodilator and inotropics were excluded from the study.

In all patients, a 7.5 Fr pulmonary artery catheter (Baxter, Irvine, California, USA.) was inserted via the right internal jugular vein or subclavian vein. Arterial and urinary catheters were placed for routine monitoring of hemodynamic parameters and renal function.

Settings in the CMV mode included a tidal volume of 8 to 10 ml/kg, and a respiration rate of 12 to 14 breaths/minute. The FiO_2 and minute volume were adjusted to maintain PaO_2 between 75 and 125 mmHg, and $PaCO_2$ between 37 and 45 mmHg in order to prevent the effects of hyper- or hypoventilation on the renal function (Hevroy and Klow, 1991). Analgesics and antibiotics were administered as needed.

Following urinary voiding, urine output of the subjects was measured for two hours without PEEP, and urine and blood samples were obtained. At one hour after the study began, the mean arterial pressure, mean pulmonary arterial pressure and pulmonary capillary wedge pressure were measured, and the cardiac index was measured by thermodilution method using an Edward cardiac output computer (Baxter, Irvine, California, USA.). One hour after administering 2 *ug*/kg/min of dopamine, mean arterial pressure, mean pulmonary arterial pressure, pulmonary capillary wedge pressure and cardiac index were measured. The urine output over the next two hours was measured and urine and blood samples were taken. The next phase of the

Table 1. Demographic characteristics of patients

No. of patients	Age	Sex	Main diagnosis	Outcome
1	67	F	Multiple trauma	Live
2	32	M	Multiple trauma	Live
3	60	F	Intestinal infarction	Live
4	38	F	Multiple trauma	Live
5	77	F	UGI bleeding	Live
6	67	M	Multiple trauma	Live
7	48	M	Necrotizing fasciatis	Live
8	53	F	Multiple trauma	Live
9	43	M	UGI bleeding	Live
10	60	F	Pneumonia	Live

experiment was delayed for 10 minutes to preclude the effect of low dose dopamine. As the PEEP was increased to 4, 8 and 12 cmH_2O at 4-hour intervals, the urine output, mean arterial pressure, mean pulmonary arterial pressure, pulmonary capillary wedge pressure and cardiac index were measured. Urine and blood samples were also taken at each interval with and without low dose dopamine administration. Sodium and creatinine contents were measured from the urine and blood samples and the creatinine clearance rate and fraction of sodium excretion were calculated by the following equation (Duke and Bersten, 1990).

Ccr = Ucr X Vu/Pcr.

FENa = (UNa/PNa)/(Ucr/Pcr) × 100

(Ccr: creatinine clearance, Ucr: urine creatinine, Pcr: serum creatinine, Vu: urine volume, UNa: urine sodium, PNa: serum sodium)

The data were expressed as mean±standard error of mean(SEM). A two way ANOVA with repeated measures was conducted using the Statview software package. The results were considered statistically significant when the p value was less than 0.05.

RESULTS

Cardiac index

Cardiac index showed 4.2 L/mim/m^2 without low dose dopamine and PEEP. It decreased with the increasing level of PEEP. At 8 cmH_2O of PEEP, the cardiac index was 3.6 L/min/m^2, a 14% reduction from the value without PEEP, with statistical significance ($p<0.01$). At 12 cmH_2O of PEEP, the cardiac index was 3.2 L/min/m^2, a 23% reduction from the value at 0 cmH_2O of PEEP, with statistical significance ($p<0.01$).

When low dose dopamine was used, the cardiac index showed 4.1 L/min/m^2 at 0 cmH_2O PEEP. At 12 cmH_2O of PEEP, the cardiac index was 3.6 L/min/m^2, an 11.3% reduction from the value without PEEP, with statistical significance ($p<0.01$).

When low dose dopamine was used, the cardiac index was significantly greater than the value without low dose dopamine at 12 cmH_2O of PEEP ($p<0.05$)(Table 2).

Mean arterial pressure

Mean arterial pressure was 102 mmHg without low dose dopamine and PEEP. The pressure tended to decrease as PEEP was increased, although the reduction was not statistically significant up to 8 cmH_2O of PEEP. At 12 cmH_2O of PEEP, mean arterial pressure was 91 mmHg, a 9.7% reduction from the value without PEEP, with statistical significance ($p<0.01$).

When low dose dopamine was used, the pressure was 103 mmHg without PEEP and it tended to

Table 2. Changes of hemodynamics

	Level of PEEP (cmH_2O)	0	4	8	12
CI	Dopamine(−)	4.2±0.2	3.9±0.1	3.6±0.1[a]	3.2±0.1[a]
	Dopamine(+)	4.1±0.2	4.0±0.4	3.9±0.4	3.6±0.2[a,c]
MAP	Dopamine(−)	102±5	100±5	93±4	91±5[a]
	Dopamine(+)	103±5	95±4	93±4	90±4[a]
MPAP	Dopamine(−)	16±2	17±2	17±3	19±3[a]
	Dopamine(+)	16±2	17±3	18±3	19±3[a]
PCWP	Dopamine(−)	10±1	9±2	11±1	12±1
	Dopamine(+)	9±1	9±1	9±1	11±1

All values are mean±SEM.

PEEP: positive end expiratory pressure (cmH_2O), CI: cardiac index(L/min/m^2), PCWP: pulmonary capillary wedge pressure(mmHg), MPAP: mean pulmonary artery pressure(mmHg), MAP: mean arterial pressure(mmHg), *a* : $p<0.01$, vs PEEP 0 cmH_2O, *c* : $p<0.05$, vs dopamine(−)

decrease as PEEP was increased, although the reduction was not statistically significant up to 8 cmH_2O of PEEP. At 12 cmH_2O of PEEP, mean arterial pressure was 90 mmHg, a 13.4% reduction from the value without PEEP, which was statistically significant ($p<0.01$).

The mean arterial pressure showed no signficant difference within the same level of PEEP (Table 2).

Mean pulmonary arterial pressure

The mean pulmonary arterial pressure was 16 mmHg at 0 cmH_2O PEEP without dopamine and when a low dose was administered. The pressure tended to increase as PEEP was increased, although the increase was not statistically significant up to 8 cmH_2O of PEEP. At 12 cmH_2O of PEEP, mean pulmonary arterial pressure was 19 mmHg, a 19% increase from the value without PEEP, with statistical significance ($p<0.01$). The mean pulmonary arterial pressure showed no statistical difference at the same level of PEEP in the absence of dopamine or when it was given at low doses (Table 2).

Pulmonary capillary wedge pressure

The pulmonary capillary wedge pressure showed no change with an increase in PEEP and no statistical difference at the same level of PEEP in the absence of dopamine or when low doses were administered (Table 2).

Urine output

Urine output was 1.6 ml/min/kg without low dose dopamine and PEEP. It tended to decrease by increasing PEEP, although the reduction was not statistically significant up to 4 cmH_2O of PEEP. At 8 cmH_2O of PEEP, urine output was 1.2 ml/min/kg, a 25% reduction from the value without PEEP, with statistical significance ($p<0.05$). At 12cmH_2O of PEEP, urine output was 0.9 ml/min/kg, a 47.3% reduction from the value without PEEP, with statistical significance ($p<0.01$).

When low dose dopamine was used, urine output was 1.6 ml/min/kg without PEEP and it tended to decrease when PEEP was increased, although this was not statistically significant up to 8 cmH_2O of PEEP. At 12 cmH_2O of PEEP, urine output was 1.2ml/min/kg, a 25% decrease from the value without PEEP, with statistical significance ($p<0.05$). When low dose dopamine was administered, the urine output was significantly increased from no dopamine at 12 cmH_2O of PEEP ($p< 0.05$) (Table 3).

Creatinine clearance

Creatinine clearance was 115 ml/min without low dose dopamine and PEEP. The clearance tended to decrease as PEEP was increased, although the reduction was not statistically significant at 4 cmH_2O of PEEP. At 8 cmH_2O of PEEP, the clearance was 97 ml/min, a 15.6% reduction from the value without PEEP, with statistical significance ($p<0.01$). At 12

Table 3. Changes in renal function

	Level of PEEP(cmH2O)	0	4	8	12
UO	Dopamine(−)	1.6±0.2	1.4±0.2	1.2±0.2[a]	0.9±0.1[b]
	Dopamine(+)	1.6±0.2	1.5±0.2	1.4±0.2	1.2±0.2[a,c]
Ccr	Dopamine(−)	115±3	103±2	97±5[a]	81±3[a]
	Dopamine(+)	119±8	112±6	103±4	109±6[c]
FENa	Dopamine(−)	1.3±0.1	1.3±0.2	1.1±0.1	1.0±0.2
	Dopamine(+)	1.3±0.1	1.2±0.1	1.2±0.1	1.1±0.1

All values are mean±SEM.
PEEP: positive end expiratory pressure, UO: urine output(mL/min/kg), Ccr: creatinine clearance(mL/min), FENa: fractional excretion of sodium (%). *a* : $p<0.01$, vs PEEP 0 cmH_2O, *b* : $P<0.05$, vs PEEP 0 cmH_2O, *c* : $p<0.05$, vs dopamine(−).

cmH_2O of PEEP, the clearance was 81 ml/min, a 30% reduction from the value without PEEP, with statistical significance ($p<0.01$).

When low dose dopamine was used, the clearance was 119 ml/min without PEEP and tended to decrease when PEEP was increased. At 12 cmH_2O PEEP, the clearance was 109 ml/min, a 9.2% decrease from the value without PEEP, without statistical significance.

When low dose dopamine was used, the creatinine clearance was significantly greater than no dopamine at 12 cmH_2O ($p<0.05$) (Table 3).

Fractional excretion of sodium (FENa)

The fractional excretion of sodium showed no change with an increase in PEEP and no statistical difference at the same level of PEEP in the absence of dopamine or when low doses were administered (Table 3).

DISCUSSION

This study showed that low dose dopamine (2 *ug*/kg/min) attenuates the reductions in cardiac output, urine output and creatinine clearance resulting at 12 cmH_2O PEEP.

Controlled mechanical ventilation using PEEP can increase the intrathoracic pressure, and it can also induce hemodynamic changes, decreasing the venous return, increasing the pulmonary vascular resistance, decreasing left ventricular function, and therefore reducing the cardiac output (Hevroy and Klow, 1991). The reduction in cardiac output can affect the renal perfusion and subsequently reduce the renal function as demonstrated by a decrease in urine output (Marquez *et al.* 1979). It has been reported that 10 cmH_2O of PEEP resulted in the reduction of urine output by 34%, GFR by 19% and renal blood flow by 32% (Annat *et al.* 1983). These results were in accordance with those of this study.

In order to prevent a reduction in cardiac and renal function resulting from the mechanical ventilation with PEEP, normal vascular volume should be maintained. Qvist *et al.* found that impaired renal function due to PEEP was not improved by fluid administration (Qvist *et al.* 1975). In this situation, low dose dopamine would be the drug of choice (Leier *et al.* 1978).

Dopamine shows various effects depending on the dosage. At dosage levels of 0.5~2.0 *ug*/kg/min, dopamine acts on the dopaminergic receptor, inducing renal vasodilation. At dosage levels of 2~5 *ug*/kg/min, it acts on beta adrenergic receptors, inducing an increase in cardiac output. At a dosage of 5*ug*/kg/min, it acts on adrenergic alpha receptors, inducing vasoconstriction.

The increase in urine output induced by low dose dopamine can be explained by direct and indirect actions on the kidney. The following four mechanisms are suggested as direct actions on the kidney: First, renal vasodilation causes increased renal perfusion which increases urine output; Second, renal blood flow passes from cortical nephrons to deep and medullary nephrons, increasing sodium excretion; Third, the increase in GFR results in an increase in solute load to proximal renal tubules; Fourth, the direct effect on the renal tubule prevents reabsorption of sodium. Indirect action of dopamine on the kidney can be explained by an increase in cardiac output and perfusion pressure. It is not known which action of low dose dopamine has more predominant effect on diuresis. Duke *et al.* reported that the use of low dose dopamine resulted in urine output without an increase in creatinine clearance rate which is the actual index of renal function(Duke *et al.* 1994). When dobutamine was used, creatinine clearance increased without increasing the urine output.

A two-hour creatinine clearance rate was selected for this study since there was little difference between the two-hour rate and the 24-hour rate when it was greater than 30 ml/min. This was for normal subjects among intensive care patients (Sladen *et al.* 1987; Martin *et al.* 1990).

When the clearance rate was lower than 30 ml/min, tubular creatinine secretion tended to result in an overestimation of the creatinine clearance rate (Luke *et al.* 1990). Therefore, accurate urine sampling was required. In this study, urine samples were taken after complete bladder voiding for accurate sampling over a short period of time.

In this study, low dose dopamine attenuated the decrease in urine output and creatinine clearance

with increasing PEEP.

The use of low dose dopamine did not change the mean arterial pressure, mean pulmonary arterial pressure, pulmonary capillary wedge pressure, or pulse rate, however it attenuated the decrease in the cardiac index with increasing PEEP. These results were in accordance with the results from other studies which reported that low dose dopamine in PEEP therapy improved cardiac output, oxygen transport and renal function in normovolemic patients (Poinsot *et al.* 1993).

It has been shown that the decrease in cardiac output by PEEP can result in a reduction in atrial natriuretic factor (Kharasch *et al.* 1988), activation of the renin-angiotensin system and an increase in antidiuretic hormone, thereby inhibiting the sodium excretion and decreasing urine output.

In this study, FENa showed no change up to 12 cmH_2O of PEEP. This may indicate that renal function is more affected by hemodynamic change than by hormonal changes up to 12 cmH_2O of PEEP, but the hormonal effect should be further studied as well.

Although many protective mechanisms of low dose dopamine on renal function have been reported, this drug may be a "double-edged sword". Dopamine may be undesirable in the "at-risk" kidney, since dopamine impairs the important tubulo-glomerular filtration mechanism, which may adversely affect the oxygen supply/demand balance; diuresis is not always associated with augmentation of renal blood flow; diuresis may mask hypovolemia or renal hypoperfusion; and, an inappropriate diuresis may produce hypovolemia (Duke and Bersten, 1990). Vascular actions by dopamine may vary according to the dosage and the individual who receives it. Pathological states such as abnormal renal function or sepsis may also complicate the response (Schwartz and Gewertz, 1988; Szerlip, 1991). Therefore, for the protection of renal function, rather than administering low dose dopamine to every patient under PEEP mechanical ventilation therapy, the disease of patients, the state of renal function and the response to low dose dopamine must be considered. If dopamine is used, greater attention must be paid to the basic elements of critical care-blood volume, renal perfusion pressure, and cardiac output-because urine output can no longer be used as a guide to the adequacy of renal blood flow (Duke and Bersten, 1990).

In conclusion, low dose dopamine attenuated the impairment of hemodynamic and renal functions brought on by controlled mechanical ventilation under PEEP up to 12 cmH_2O.

REFERENCES

Annat G, Viale JP, Xuan BB, Hadj AO, Benzoni D, Vincent M, Gharib C, Motin J: Effect of PEEP ventilation on renal function, plasma renin, aldosterone, neurophysins and urinary ADH and prostaglandins. *Anesthesiology 58: 136-141, 1983*

Duke GJ, Bersten AD: Dopamine and renal salvage in the critically ill patient. *Anaesth Intensive Care 20: 277-287, 1990*

Duke GJ, Briedis JH, Weaver RA: Renal support in critically ill patients, low dose dopamine or low dose dobutamine? *Crit Care Med 22: 1919-1925, 1994*

Hevroy O, Klow NE: Left ventricular diastolic function during short term positive end expiratory pressure in dogs. *Acta Anesthesiol Scand 35: 333-338, 1991*

Kharasch ED, Yeo KT, Kenny MA, Buffington CW: Atrial natriuretic factor may mediate the renal effects of PEEP ventilation. *Anesthesiology 69: 862-869, 1988*

Leier CV, Heban PT, Huss P, Bush CA, Lewis RP: Comparative systemic and regional hemodynamic effects of dopamine and dobutamine in patients with cardiomyopathic heart failure. *Circulation 58: 466-475, 1978*

Luke DR, Halstenson CE, Opsahl JA: Validity of creatinine clearance estimates in the assessment of renal function. *Clin Pharmacol Ther 48: 503-508, 1990*

Marquez JM, Douglas ME, Downs JB, Wu WS, Mantini EL, Kuck EJ, Calderwood HW: Renal function and cardiovascular responses during positive airway pressure. *Anesthesiology 50: 393-398, 1979*

Martin C, Alaya M, Jaques B, Saux P, Goulin F: Assessment of creatinine clearance in intensive care patients. *Crit Care Med 18: 1224-1226, 1990*

Poinsot O, Ramond JA, Farve H, Sulter PM: Fenoldopam improves renal hemodynamics impaired by positive end expiratory pressure. *Anesthesiology 79: 680-684, 1993*

Qvist J, Pontoppidan J, Wilson RS, Lowenstein E, Laver MB: Hemodynamic response to mechanical ventilation with PEEP: the effect of hypervolemia. *Anesthesiology 42:45-55, 1975*

Schwartz LB, Gewertz BL: The renal response to low dose dopamine. *J Surg Res 45: 574-588, 1988*

Sladen RN, Endo E, Harison T: Two-hour versus 24 hour creatinine clearance in critically ill patients.

Anesthesiology 67: 1013-1016, 1987

Szerlip HM: Renal dose dopamine: Fact and fiction. *Ann Intern Med 115: 153-154, 1991*

Venus B, Mathru M, Smith RA, Pham CG, Shirakawa Y, Sugura A: Renal function during application of positive end expiratory pressure in swine: effects of hydration. *Anesthesiology 62: 765-769, 1985*