

## ***Fenoldopam Improves Renal Hemodynamics Impaired by Positive End-Expiratory Pressure***

O. Poinot, M.D.,\* J-A. Romand, M.D.,† H. Favre, M.D.,‡ P. M. Suter, M.D.§

**Background:** Mechanical ventilation with positive end-expiratory pressure (PEEP) can impair renal hemodynamics. Fenoldopam, a dopamine receptor agonist, has been shown, in animal experiments, to improve renal perfusion. The purpose of the current study was to examine the effects of this agent on altered renal hemodynamics secondary to positive pressure ventilation.

**Methods:** Twelve patients requiring mechanical ventilation of their lungs and PEEP for the treatment of hypoxemia after multiple trauma or visceral surgery were studied. Hemodynamic variables, renal vascular resistance, urine flow, creatinine, inulin and PAH clearance, and excretion of sodium and potassium (NaE and KE) were measured before and after introduction of a level of PEEP high enough to decrease urine flow rate by 25% or more, and after administration of intravenous fenoldopam.

**Results:** No hemodynamic effect resulted from  $0.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , but  $0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  fenoldopam decreased both diastolic and mean arterial blood pressure from  $66 \pm 37$  (mean  $\pm$  SEM) to  $57 \pm 21$  mmHg, and from  $83 \pm 3$  to  $74 \pm 4$  mmHg, respectively. Renal vascular resistance was reduced from  $54 \pm 12$  to  $19 \pm 5$  dynes  $\cdot \text{s} \cdot \text{cm}^{-5}$  at  $0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . Fenoldopam produced a dose-related increase in renal blood flow and PAH clearance. With  $0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  fenoldopam, urine flow increased from  $81 \pm 25$  to  $116 \pm 29$  ml/h, NaE from  $28 \pm 7$  to  $85 \pm 70$   $\mu\text{M}/\text{min}$ , and KE from  $65 \pm 12$  to  $109 \pm 16$   $\mu\text{M}/\text{min}$ .

**Conclusions:** The results of the current study indicate that intravenous fenoldopam at a dose of  $0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  improves renal hemodynamics and increases Na and K excretion in patients requiring mechanical ventilation of their lungs and PEEP. These effects are probably caused by an increased kidney perfusion secondary to renal artery vasodilation. (Key words: Kidney; potassium urinary excretion; sodium urinary

excretion; renal blood flow; renal vascular resistance. Receptors: dopamine-1.)

MECHANICAL ventilation and positive end-expiratory pressure (PEEP) are often used to improve pulmonary gas exchange in patients with acute respiratory insufficiency. However, this ventilatory technique may induce hemodynamic and hormonal changes that, in turn, may lead to vital organ dysfunction, such as oliguria.<sup>1-2</sup> Changes in renal perfusion pressure and intrarenal distribution of blood flow, as well as mediator-related activity, such as that caused by atrial natriuretic peptide<sup>3</sup> and the renin-angiotensin system,<sup>4</sup> are involved in this effect. Intravenous volume expansion or dopamine administration may prevent or improve acute renal dysfunction in this situation.<sup>1,5</sup> Fluid administration, however, can worsen pulmonary function. The action of dopamine is mediated by the dopaminergic receptors DA-1, which have been identified in the renal arterioles, proximal tubules, and glomeruli.<sup>6-7</sup> However, dopamine is also an agonist of  $\alpha$  and  $\beta$ -1 receptors. The lack of selectivity of dopamine for intrarenal DA-1 receptors often causes undesirable cardiovascular effects, such as tachycardia, limiting its use in patients whose lungs are being mechanically ventilated.<sup>8</sup>

A selective dopaminergic receptor DA-1 agonist would be more suitable for treating the renal side effects of positive pressure ventilation by enhancing renal blood flow and increasing urinary sodium excretion. Fenoldopam, a derivative benzazepine molecule ([6-chloro-2,3,4,5-tetrahydro-1,4-hydroxyphenol]1H-3-benzazepine 7,8-diol, methane sulfonate) is such an agent. Indeed, fenoldopam is a specific agonist of postsynaptic dopaminergic DA-1 receptors<sup>9</sup> without  $\alpha$ ,  $\beta$ -1, or dopaminergic A-2 (DA2) activity.<sup>8</sup> Fenoldopam has no effect on the central nervous system, presumably because of its inability to penetrate the blood-brain barrier in relation to a polar group on the molecule.

Although fenoldopam is used for the treatment of hypertension, its effects are still controversial.<sup>10-13</sup> It is, however, a potent renal artery vasodilator in animals

\* Resident, Division of Surgical Intensive Care.

† Chief Resident, Division of Surgical Intensive Care.

‡ Associate Professor, Division of Nephrology.

§ Associate Professor, Division of Surgical Intensive Care.

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Address reprint requests to Dr. Suter: Chairman, Department of Anesthesiology, Hôpital Cantonal Universitaire, 1211 Genève 14, Switzerland.

## FENOLDOPAM IMPROVES RENAL HEMODYNAMICS

and in humans, acting *via* selective stimulation of renal dopaminergic receptors,<sup>14</sup> inducing an intracellular increase of the adenylate cyclase-mediated cyclic AMP concentration.<sup>15</sup> Furthermore, in a dog model, the renal artery vasodilation induced by fenoldopam is three times greater than that produced by dopamine.<sup>8</sup>

Such potent and selective renal artery vasodilation could be useful in treating the renal hemodynamic effects induced by mechanical ventilation with PEEP,<sup>5</sup> in which impaired renal perfusion seems to play an important role.

The purpose of the current study was to investigate the effects of two different doses of fenoldopam given by intravenous infusion on renal function variables and hemodynamics during positive pressure ventilation before and after introduction of PEEP.

## Materials and Methods

Twelve patients, 10 men and 2 women, mean age 59 yr (range 29–70 yr), admitted to our surgical intensive care unit, were investigated. All had an arterial, central venous, and urinary catheter in place for routine monitoring of vital signs. In three patients, a pulmonary artery catheter had been inserted for clinical monitoring. The patients studied were admitted to the ICU after multiple trauma ( $n = 3$ ; without spinal or kidney involvement), after extensive abdominal surgery ( $n = 2$ ; without kidney involvement), or after thoracic surgery ( $n = 7$ ). No patient had prior acute or chronic kidney disease.

Entry criteria for the study were as follows: 1) increased alveoloarterial pressure gradient for oxygen, necessitating an inspired oxygen fraction ( $FI_{O_2}$ ) of more than 0.5 and mechanical ventilation; and 2) hemodynamic stability assessed by a maximal change of 10% in heart rate, blood pressure, and diuresis, as well as minimal bleeding *via* drains ( $<50$  ml/h) to avoid variations in hematocrit during the hour before the beginning of the study and during the study itself.

Exclusion criteria were the following: hypovolemia (assessed by hemodynamics), pregnancy, uncontrollable ventricular arrhythmia, acute or chronic renal failure, hyponatremia, thrombocytopenia  $< 75,000/mm^3$ , hypophosphatemia, and requirement of catecholamines, diuretics, dopamine antagonists, or vasodilators in the 3 h preceding the study period.

Informed consent was obtained from the patient or, if this was impossible because of the clinical condition, from the patient's closest relative or personal physician.

The study protocol was submitted to and approved by the Committee for Ethics in Human Research of our institution.

Volume-controlled ventilators were used in the assist/control mode to deliver tidal volumes of 12 ml/kg body weight. During the entire study,  $FI_{O_2}$  and minute ventilation were adjusted to maintain arterial oxygen tension ( $Pa_{O_2}$ ) between 10 and 15 kPa (75 and 112.5 mmHg) and arterial carbon dioxide tension ( $Pa_{CO_2}$ ) between 5 and 6 kPa (37.5 and 45 mmHg) to avoid the effects of hyper- or hypoventilation on renal function.<sup>16</sup> The study was performed during two ventilatory conditions using the same sequences: first, intermittent positive-pressure ventilation (IPPV) for 1 h (baseline); second, PEEP was added (continuous positive pressure ventilation, CPPV) at 4 cmH<sub>2</sub>O for 1 h. If urine flow rate (UFR) did not decrease by at least 25% in the second hour, PEEP was again increased by 4 cmH<sub>2</sub>O for 1 h. The highest PEEP allowed was 12 cmH<sub>2</sub>O.

After a 1-h measurement period at the PEEP level associated with a decrease in UFR of 25% or more, fenoldopam  $0.1 \mu g \cdot kg^{-1} \cdot min^{-1}$  was administered intravenously for 1 h, and all hemodynamic and renal function variables were recorded. Fenoldopam was then increased to  $0.2 \mu g \cdot kg^{-1} \cdot min^{-1}$  during the next hour, and the measurements were repeated. Fenoldopam was then stopped, and all variables were recorded again 1 h after the end of fenoldopam infusion, at the same level of PEEP as during drug infusion.

We considered the CPPV as the control condition to be compared with three other conditions: CPPV and fenoldopam  $0.1 \mu g \cdot kg^{-1} \cdot min^{-1}$ ; CPPV and fenoldopam  $0.2 \mu g \cdot kg^{-1} \cdot min^{-1}$ ; and CPPV 1 h after stopping fenoldopam.

Hemodynamics were measured at the end of each 1-h condition. Cardiac index was measured in the three patients equipped with a pulmonary artery catheter.

All concomitant medication, such as sedatives or muscle relaxants, were administered according to clinical needs, and their dosages were kept constant during all study periods. Intravenous infusion of glucose 10% was kept constant at  $2 ml \cdot kg^{-1} \cdot h^{-1}$ .

Blood and urine samples were taken at the end of each hour of the protocol described above. Sodium, K, and creatinine were measured by standard methods; inulin and paraaminohippuric acid (PAH) were determined by colorimetric spectrophotometry<sup>17</sup> after intravenous infusion and when a steady state plasma concentration had been achieved. All variables and calculations were obtained every hour.

### Renal Function Variables

Glomerular filtration rate (GFR) was determined by inulin and creatinine clearance ( $C_{in}$ ,  $C_{cr}$ ), and renal plasma flow (RPF) by PAH clearance ( $C_{PAH}$ ). Renal vascular resistance (RVR) was calculated as mean arterial pressure (MAP) divided by renal blood flow ( $MAP/RPF \cdot (1 - \text{hematocrit})^{-1}$ ). Filtration fraction (FF) was obtained by dividing  $C_{in}$  by  $C_{PAH}$ .

Data were analyzed on a Macintosh SE personal computer (Apple Computer, Cupertino, CA), and statistical analysis was made using the Kruskal-Wallis test for nonparametric data.<sup>18</sup>

### Results

All patients presented a 25% or more decrease in urine output after the introduction of PEEP. In eight patients, this occurred at 4 cmH<sub>2</sub>O of PEEP; in two patients, it occurred at 8 cmH<sub>2</sub>O; and in two patients, it occurred at 12 cmH<sub>2</sub>O. No clinically important side effects were noted in the 12 patients studied. The data are presented as mean  $\pm$  SEM in table 1 and figure 1. No changes were noted in pulse rate.

No significant changes were noted in the renal hemodynamic variables measured with fenoldopam at a dose of 0.1  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , except for RVR (see below). However, a significant change in urinary excretion of Na and K was observed. Fenoldopam, 0.2  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , increased  $C_{PAH}$  (reflecting RPF) from  $216 \pm 65$  to  $503 \pm 152 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^2^{-1}$  ( $P < 0.01$ ).

Filtration fraction decreased from  $34 \pm 4$  before fenoldopam to  $28 \pm 3$  and  $26 \pm 4\%$  at 0.1 and 0.2

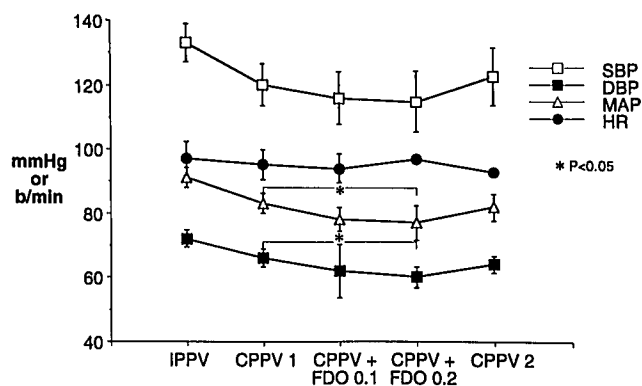


Fig. 1. Hemodynamic changes induced by positive end-expiratory pressure and fenoldopam. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) during IPPV and CPPV before, during, and after the two dosages of fenoldopam (0.1 and 0.2  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ). Values are mean  $\pm$  SEM.

$\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  fenoldopam, respectively ( $P < 0.01$  for comparison between CPPV and both dosages of fenoldopam), but urine flow rate, creatinine clearance, and sodium and potassium excretion increased significantly. Renal vascular resistance decreased from  $54 \pm 12$  to  $30 \pm 7 \text{ dynes} \cdot \text{s} \cdot \text{cm}^{-5}$  with 0.1  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  and to  $19 \pm 4 \text{ dynes} \cdot \text{s} \cdot \text{cm}^{-5}$  with 0.2  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  intravenous fenoldopam, respectively ( $P < 0.05$  and  $P < 0.01$ , respectively).

### Discussion

The current study shows that fenoldopam can improve renal hemodynamics when these have been im-

Table 1. Renal Function Variables Determined in 12 Patients

	IPPV	CPPV <sub>1</sub>	CPPV + Fenoldopam 0.1 ( $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ )	CPPV + Fenoldopam 0.2 ( $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ )	CPPV <sub>2</sub>
RVR ( $\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}$ )	49 $\pm$ 11	54 $\pm$ 12	30 $\pm$ 7*	19 $\pm$ 4*	22 $\pm$ 4*
UFR (ml/h)	162 $\pm$ 49	81 $\pm$ 24	75 $\pm$ 22	116 $\pm$ 29*	65 $\pm$ 8*
$C_{CR}$ ( $\text{ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^2^{-1}$ )	99 $\pm$ 15	65 $\pm$ 11	83 $\pm$ 11	115 $\pm$ 20*	97 $\pm$ 14
$C_{IN}$ ( $\text{ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^2^{-1}$ )	78 $\pm$ 22	72 $\pm$ 22	72 $\pm$ 22	111 $\pm$ 33	98 $\pm$ 30
$C_{PAH}$ ( $\text{ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^2^{-1}$ )	258 $\pm$ 53	216 $\pm$ 65	272 $\pm$ 82	503 $\pm$ 152*	449 $\pm$ 136*
Filtration fraction (%)	35 $\pm$ 6.1	34 $\pm$ 4.2	28 $\pm$ 3.4	26 $\pm$ 3.9*	27 $\pm$ 4.6*
U Na excretion (Umol/min)	189 $\pm$ 44	28 $\pm$ 7	74 $\pm$ 36	85 $\pm$ 70*	80 $\pm$ 27*
U K excretion (Umol/min)	103 $\pm$ 15	66 $\pm$ 12	80 $\pm$ 14	109 $\pm$ 16*	84 $\pm$ 16*

Values are mean  $\pm$  SEM.

IPPV = intermittent positive-pressure ventilation; CPPV<sub>1</sub> = continuous positive-pressure ventilation before fenoldopam; CPPV = continuous positive-pressure ventilation; CPPV<sub>2</sub> = continuous positive-pressure ventilation after fenoldopam; RVR = renal vascular resistance; UFR = urine flow rate;  $C_{CR}$  = creatinine clearance;  $C_{IN}$  = inulin clearance;  $C_{PAH}$  = paraaminohippuric acid clearance; U Na = urinary sodium; U K = urinary potassium.

\*  $P < 0.05$  compared to CPPV<sub>1</sub>.

## FENOLDOPAM IMPROVES RENAL HEMODYNAMICS

paired by mechanical ventilation with PEEP. Intravenous fenoldopam resulted in a marked decrease in renal vascular resistance and an increase in renal plasma flow, diuresis, natriuresis, and kaliuresis. Fenoldopam,  $0.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , had only marginal hemodynamic effects, indicating that the effective clinical dosage is  $0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ .

In our study,  $0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  fenoldopam acted as a potent systemic and renal vasodilator, probably by stimulating renal vascular DA1 receptors. Fenoldopam produced an 86% increase in renal plasma flow and a 24% decrease in filtration fraction (table 1). Despite this substantial increase in renal plasma flow, there was no significant change in the glomerular filtration rate. The discrepancy between inulin and creatinine clearance indicates that fenoldopam dilates both afferent and efferent arterioles,<sup>19</sup> probably with a stronger action on efferent glomerular arterioles, as suggested by Hughes *et al.*<sup>20</sup> At a dosage of  $0.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , fenoldopam increased sodium and potassium excretion. At  $0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , sodium excretion increased by 300% and potassium excretion by 65% (table 1).

We postulate that the dilatation of efferent arterioles by fenoldopam may cause a reduction of proximal tubular sodium and water reabsorption, and a concomitant increase in distal sodium reabsorption, as described above. Once the capacity of the loop of Henle and the collecting tubules to increase distal sodium reabsorption was exceeded, natriuresis and diuresis ensued.

Several mechanisms may be responsible for the natriuretic and diuretic actions of fenoldopam. First, these actions may be caused entirely by renal vasodilation, because a higher renal plasma flow associated with a reduced filtration fraction may result in decreased proximal tubular sodium reabsorption by altering peritubular capillary hydrostatic and oncotic pressures, as demonstrated by Brenner *et al.*<sup>21</sup> This hypothesis is reinforced by the hemodynamic measurements obtained in the three patients with a pulmonary artery catheter, which show an increased cardiac index with fenoldopam infusion. Second, change in blood flow to the medullary and deep nephrons, resulting in a "washout" of the renal medulla, may also enhance sodium excretion.<sup>22</sup> However, Hardaker and Wechsler<sup>23</sup> showed that DA-1 receptor stimulation may redistribute the renal plasma flow from the superficial to the sodium- and water-avid juxtamedullary nephrons, which would result in a decrease, not an increase, in sodium excretion. This, however, is unlikely because of the

brief duration of our investigation. Third, an increased solute load entering the proximal tubule, because of an increase in glomerular filtration rate, may explain the natriuresis; however, in our study, no significant increase in glomerular filtration rate was observed. Finally, fenoldopam may exert a direct effect on the renal tubules, particularly at the distal level,<sup>24</sup> to prevent reabsorption of sodium, as suggested by Knox.<sup>25</sup> Fenoldopam improves renal function in rats with cyclosporin A-induced renal failure,<sup>26</sup> as well as in dogs with spontaneous renal failure.<sup>14</sup> DA-1 receptor stimulation causes an increase in RPF, and natriuresis can be increased by stimulation of tubular DA-1 receptors.<sup>27</sup>

In the current study, the increased renal plasma flow may explain the increase in sodium excretion. However, the time course of renal plasma flow and sodium excretion changes also indicates a possible tubular mechanism. Indeed, after fenoldopam was stopped, sodium excretion decreased toward control values, but renal plasma flow remained significantly increased for another hour. If the increase in renal plasma flow alone had been responsible for the natriuresis, then sodium excretion should have decreased in parallel to the decrease in RPF. This dissociation raises the possibility that fenoldopam directly inhibits tubular sodium reabsorption.

An important limitation of our study was that cardiac output was measured in only 25% of the patients. In these patients, an increase in cardiac output was seen after introduction of fenoldopam. An alternative explanation for the correction of the renal hemodynamic effects of PEEP may be related to the afterload reduction induced by this drug. Further studies are needed to clarify this point.

In conclusion, continuous intravenous infusion of the dopaminergic DA-1 agonist fenoldopam produced a marked improvement in kidney hemodynamics, restoring diuresis in patients requiring mechanical ventilation of their lungs and PEEP. These effects are probably caused by direct renal vasodilation, as well as a possible direct action on tubular DA-1 receptors of fenoldopam.

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