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THE EVALUATION OF THE POSSIBLE EFFECT OF POSITIVE END EXPIRATORY PRESSURE (PEEP) ON PHARMACOKINETICS OF PHENYTOIN IN PATIENTS WITH ACUTE BRAIN INJURY UNDER MECHANICAL VENTILATION.

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ABSTRACT

Positive ventilation has shown to have an influence on pharmacokinetic and disposition of some drugs. Because phenytoin with a narrow therapeutic range, is the most commonly used drug for prophylaxis and treatment of early seizures after acute brain injuries, in the present study the effect of short term PEEP (5-10 cm H₂O for at least 8 hours) on phenytoin serum concentration and pharmacokinetic parameters such as V_{max} and clearance in brain injured patients under mechanical ventilation was examined. Ten patients with moderate to severe acute brain injury who were placed on mechanical ventilation with an initial PEEP level of 0-5 cm H₂O were included in the study. Patients received phenytoin loading dose of 15 mg/kg followed by a maintenance daily dose of 3-7 mg/kg initiated within 12 hours of loading dose. Samples were taken on two different occasions before and after PEEP elevation. Total phenytoin serum concentrations were determined by HPLC method. A time invariant Michaelis-Menten pharmacokinetic model was used to calculate V_{max} and clearance for each patient. Derived variables were calculated as follows: V_{max}, 3.5-6.8 and 3.7-8.2 mg/kg/day; Clearance, 0.1-0.7 and 0.1-1.2 l/kg/day (before and after PEEP elevation, respectively). Our data have shown a wide range of variability (2.6-32.5 mg/l) in phenytoin serum concentrations. There were no statistically significant differences in the measured total concentrations (p=0.721) and calculated V_{max} and clearance (p=0.285) before and after PEEP elevation. Administration of fluid and inotropic agents, limitation in application of higher levels of PEEP and drug interactions, shall be considered as possible explanations for these findings.

Keywords: Acute brain injury, PEEP, Phenytoin, Pharmacokinetic

INTRODUCTION

Seizures are common during the early phase following a stroke and have been reported to occur with a frequency of 2.4-6% within 14 days afterward (1-4). Phenytoin is commonly and widely used anticonvulsant drug in critically ill patients (5) and is being considered as a drug of choice for prophylaxis and treatment of seizures post-brain injury (6,7).

In most patients with cerebrovascular events, significant respiratory problems do not occur but when present, they may be a marker of severe derangement. In fact respiratory arrest represents

primary cause of death in the first few days after a stroke (8). The ventilatory management of patients with diffuse acute lung injury (e.g., ARDS) requires mechanical ventilation. According to a recent study, 10% of unselected stroke patients require mechanical ventilation during their hospital stay (9). In this setting, adequate arterial oxygen saturation is usually achieved by raising the inspired oxygen fraction (FiO₂) and increasing the end expiratory lung volume to recruit collapsed or flooded alveoli. This can be achieved by addition of extrinsic positive end-expiratory pressure (PEEP) (10,11).

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PEEP is a mode of therapy which is used in conjunction with mechanical ventilation whenever in spite of administration of 100 percent oxygen, there is still inadequate oxygenation (10). Mechanical ventilation with PEEP is a well-documented cause of reduction in cardiac output, renal flow, glomerular filtration rate and urine flow (12-14). Also, it has been shown that PEEP is associated with decrease in hepatic and/or portal blood flow as well (15-17). Therefore, it has been theorized that the pharmacokinetics of drugs that are predominantly eliminated through the liver might be substantially affected following positive ventilatory supports measures (18).

While alteration in pharmacokinetic parameters of some drugs such as lidocaine (19), amikacin (20) and aminophylline (21) by PEEP have been reported, the contribution of mechanical ventilation in alteration of phenytoin clearance is unknown and has not yet been quantified.

On the other hand, in vitro studies on oxidatively metabolized drugs such as propranolol and theophylline have shown that hypoxic conditions (Even by relatively minor reductions in oxygen supply, of a magnitude likely to be encountered in vivo) and oxygen supplementation may result in impairment or restoration of oxidative metabolism of these drugs, respectively (22-24).

Because phenytoin elimination performs almost entirely through hepatic oxidation (by cytochrome P450 (CYP) 2C9 and CYP2C19 as principle enzymes), it is expected that the hepatic oxidative metabolism of phenytoin should be influenced by alteration in oxygenation or conditions that alter hepatic oxygenation. This may be of special attention in regard to PEEP because while its use improves oxygenation and treats acute pulmonary failure, it may contribute to mesenteric ischemia due to alteration in regional blood flow.

Phenytoin has a relatively narrow therapeutic range of serum concentrations, 40-80 $\mu\text{mol/l}$ (10-20 mg/l), and is known to show concentration-dependent kinetics within this therapeutic range. Because of the fact that, small changes in dose and minor alterations in hepatic metabolism of phenytoin may cause a disproportionately large effect on serum concentrations, in this study it was intended to examine whether the application of PEEP in levels usually used for brain injured patients could have influences on the pharmacokinetic profile of phenytoin in these patients? and if so, will there be a need for dosing adjustment in this setting?

METHODS

The study was conducted at trauma/neurosurgical ICU of Sina Hospital. Fifteen male or nonpregnant female patients aged 18 or older who

had moderate to severe acute brain injury defined as Glasgow Coma Scale score (GCS) ≤ 12 , requiring intravenous phenytoin for treatment or prophylaxis of post injury seizures and also were required mechanical ventilation with a PEEP level of 5-10 cm H₂O due to respiratory failure and PaO₂/FiO₂ < 300 mmHg (e.g., Acute Lung Injury), were included in the study. The study protocol was approved by the ethical committee of Tehran University of Medical Sciences.

Patients were excluded if any one of the following was present:

Bradycardia, second- or third degree heart block, clinically important hypotension, laboratory evidences of preexisting hepatic or renal disease (i.e., total bilirubin > 2 mg/dl, ALT > 3 times of normal, serum creatinine > 2 mg/dl), history of phenytoin administration and hypersensitivity to phenytoin.

The use of medications which are known to affect the phenytoin metabolism (cimetidine, corticosteroids, chloramphenicol, phenobarbital) or alter its protein binding (warfarin, aspirin, heparin, tolbutamide, valproic acid, or a sulfonamide) were restricted throughout the study.

Drug administration and sampling:

Patients received an IV loading dose of 15 mg/kg of phenytoin sodium (50 mg/ml, Daru-Pakhsh, Iran) at a maximum rate of 50 mg/min followed by a maintenance dose of 3-7 mg/kg/day divided into three doses, administered at 8 hours intervals. Each dose was diluted in 0.9% saline and administered over 30 minutes by means of a controlled infusion pump at an infusion rate that did not exceed 50 mg/min.

Two blood samples were collected at trough levels (30 min before the next dose), first after at least 3 days (completion of 9 doses) of phenytoin administration when patients were either extubated or under mechanical ventilation with initial PEEP level of 0-5 cm H₂O, and the second, at least 8 hours after PEEP elevation to 5-10 cm H₂O. Blood samples were obtained from an indwelling arterial or central venous catheters whenever possible or by venipuncture.

Measurements

The severity of the condition of each patient was globally characterized by the use of the Acute Physiology and Chronic Health Evaluation (APACHE) II score (25). This score is routinely calculated within the first 24 hrs of the patient's intensive care unit admission. In this study, the APACHE II score was also computed at each time that phenytoin serum concentrations were measured. Evidence of misadventure or seizures during phenytoin therapy was determined by

direct investigator observation and daily concurrent review of medical record. Continuous monitoring of the electrocardiogram with lead II, systolic, diastolic, mean arterial pressure (MAP), heart rate, central venous pressure (CVP) and pulse oxymetry were accomplished in accordance with ICU protocol. Respiratory parameters such as arterial oxygen pressure (PaO₂), PaO₂/FiO₂, oxygen saturation (SpO₂), at each sampling time, before and after PEEP elevation were reported. Central venous pressure (CVP) was also monitored every 3 hours. Serum albumin concentrations were measured before therapy and within 24 hours of the serum phenytoin concentration measurements.

Drug assay procedure

Blood samples were allowed to clot and were centrifuged at room temperature for 15 minutes at 3000 rpm. The serum was transferred and stored at -20°C until final assay.

An HPLC method was developed for the analysis of total phenytoin serum concentrations. One hundred µl of serum samples were precipitated by addition of two fold volume of methanolic solution of phenacetin (5 µg/ml) as internal standard. Fifty µl of supernatant was injected into a Spherimage C18 column (5 µm, 250×4 mm, Knauer, Germany) through a rheodyne injector fitted by a 50 µl loop. Analysis was performed by using a high pressure pump k-1001 and k-2600 UV spectrophotometer (all from Knauer, Germany). Phosphate buffer (pH=7); acetonitril: methanol (57:22:21) were used as mobile phase with flow rate of 1 ml/min and the eluent was monitored at 220 nm.

Unknown phenytoin concentrations were determined by the application of unweighted least-squares regression analysis of peak-height ratios of phenytoin to internal standard as function of the concentration of the standards ranging from 1.73 to 29.62 µg/ml (r²= 0.999). The limit of detection for phenytoin assay was 0.05 µg/ml. The coefficient of variation for intra- and inter-day assays for total phenytoin concentrations was less than 7% (2.4-6.7%). The recovery (mean±SD) of phenytoin was 91±5%.

Pharmacokinetic and Statistical Analysis

A Michaelis-Menten pharmacokinetic model was used to calculate maximum rate of metabolism (V_{max}) and Clearance (Cl) of phenytoin for each sampling time. Michaelis-Menten constant (k_m) was set at 4 mg/l (26).

Winter-Tozer method (Equation I) was used to calculate adjusted total phenytoin concentration (dphET) based on the albumin concentration (Alb) (27).

$$\text{dphET} = \text{dphT} / (\text{Alb}(\text{g/dl}) \times 0.2) + 0.1 \quad (\text{Equation I})$$

Where dphT is measured total phenytoin concentration.

Results of a study on 17 neurosurgical patients (28) showed that the Sheiner-Tozer equation (26) provides an unbiased and precise clinical estimate of measured free phenytoin concentration (dphF) in patients for whom dphF is unavailable or impractical. This equation (No II) was used to estimate free phenytoin concentration (dphEF) based on (dphT) in present study.

$$\text{dphEF} = [\text{dphT} / (\text{Alb}(\text{g/dl}) / 4.4) \times (0.9 + 0.1)] \times 0.1 \quad (\text{Equation II})$$

Adjusted total serum concentrations (dphET) were used for estimation of V_{max} and clearance.

A non-parametric method (wilcoxon signed rank test) was used to compare pharmacokinetic and respiratory parameters before and after PEEP elevation. A p value of <0.05 was considered statistically significant. Data are represented as mean ±SE.

RESULTS

Of 15 patients, who were enrolled in the study, 10 (6 men and 4 Women) aged 55–81 years (mean 67.7) completed the study protocol. Five patients were excluded from the study: one patient was expired before completion of the study time, one patient was transferred elsewhere, two patients had early extubation and one patient was excluded due to variations in PEEP levels.

Demographic characteristics and concomitant drug therapy which potentially interfere with phenytoin disposition for each patient are listed in Table 1. Phenytoin maintenance doses, APACHE II scores at sampling times, measured total phenytoin concentrations (dphT), estimates of total (dphET) and free (dphEF) phenytoin concentrations before and after PEEP elevation are provided in Table 2.

Albumin concentrations, estimates of V_{max} and Cl, initial and final levels of PEEP for each patient before and after PEEP elevation are summarized in Table 3.

There were no statistically significant differences between the measured total concentrations (dphT) before and after PEEP elevation (p=0.721). The difference observed between pre- and post-PEEP values of V_{max} and Cl were not also significant (p=0.285 for both variables).

While there were no significant difference between values of PaO₂ and SpO₂ before and after PEEP elevation (125±16 versus 149±15, p=0.285 and 96±0.85 versus 98±0.64, p=0.153, respectively), a trend in increase of these parameters was observed. The PaO₂/FiO₂ ratio showed a significant improvement after PEEP elevation (p=0.021) (Figure 1). Application of

Table1. Patients Demographics and Clinical Data

Patient No.	Age (years)	gender	weight (Kg)	Admission GCS	APACHE II 1 st 24h	Diagnosis	Concomitant Medications*	Outcome
1	55	F	70	8	22	ICH	Dxm (7)	Died
2	55	M	60	11	18	Ischemic Stroke		D/C
3	68	F	70	5	27	ICH,IVH	Dxm (7)	Died
4	56	M	70	4	29	MVA	Dxm (8), Chlm(2)	Died
5	78	M	75	10	26	SDH		Died
6	65	F	85	4	28	ICH,IVH	Phb**(10), Dxm(3)	Died
7	81	M	55	7	31	ICH		Died
8	81	F	60	6	26	Ischemic Stroke	Cmt (2), Phb (1)	Died
9	73	M	85	7	22	Ischemic Stroke	Phb (10), Dxm(9)	D/C
10	65	M	80	7	19	ICH,IVH	Cmt (5)	Died

GCS = Glasgow Coma Score; APACHE = Acute Physiologic and Chronic Health Evaluation; ICH = intracerebral hemorrhage; intraventricular hemorrhage; SDH = subdural hemorrhage; MVA = motor vehicle accident; Dxm = dexamethasone; Chlm = chloramphenicol; Phb = phenobarbital; Cmt = cimetidine; D/C = discharged. * medications that could alter phenytoin metabolism. Number in parentheses indicates duration of therapy. ** discontinued 8 days before sampling.

Table2. Comparison of Measured and Estimated Phenytoin Concentrations Before and After PEEP Elevation

Patient No.	Before PEEP Elevation					After PEEP Elevation			
	PHT MD (mg/kg/day)	dphT	dphET	dphEF	APACHE II	dphT	dphET	dphEF	APACHE II
1	3.2	14.2	23.6	2.3	17	11.2	15.1	1.5	22
2	5.0	11.5	11.7	1.1	13	11.7	11.9	1.2	14
3	4.3	14.1	17.2	1.7	22	16.6	20.3	2.0	30
4	4.3	19.5	22.2	2.2	14	28.6	32.5	3.2	18
5	4.0	10.5	10.3	1.0	23	4.3	4.2	0.4	24
6	3.5	8.7	9.2	0.9	22	8.8	9.4	0.9	17
7	5.4	17.6	27.6	2.8	21	15.2	23.8	2.3	26
8	5.0	5.4	8.2	0.8	23	4.8	7.3	0.7	16
9	3.5	3.6	4.8	0.5	19	1.9	2.6	0.3	20
10	3.7	12.1	20.8	2.0	18	13.1	22.6	2.2	22
Mean ±SE	4.2 ±0.2	11.7 ±1.6	15.6 ±2.4	1.5 ±0.2	19.2 ±1.1	11.6 ±2.4	14.9 ±3.1	1.5 ±0.3	20.9 ±1.5

PHT MD = phenytoin maintenance dose; PEEP = positive end expiratory pressure; dphT = measured total phenytoin concentration; dphET = adjusted total phenytoin concentration; dphEF = estimated free phenytoin concentration; APACHE II = acute physiologic and chronic health evaluation II.

Table3. Comparison of Pharmacokinetic Parameters of Phenytoin Before and After PEEP Elevation

Patient Number	Before PEEP Elevation				After PEEP Elevation		
	Albumine (g/dl)	Initial PEEP (cm H ₂ O)	V _{max} * (mg/kg/day)	Cl* (L/kg/day)	Final PEEP (cm H ₂ O)	V _{max} * (mg/kg/day)	Cl* (L/kg/day)
1	2.5	0	3.5	0.1	8	3.7	0.2
2	4.4	0	6.2	0.4	5	6.1	0.4
3	3.6	3	4.9	0.2	8	4.7	0.2
4	3.9	3	4.6	0.2	8	4.4	0.1
5	4.6	5	5.1	0.3	10	7.2	0.9
6	4.2	5	4.6	0.3	10	4.6	0.3
7	2.7	3	5.7	0.2	10	5.9	0.2
8	2.8	3	6.8	0.6	10	7.1	0.6
9	3.2	5	5.9	0.7	10	8.2	1.2
10	2.4	3	4.1	0.2	10	4.1	0.1
Mean±SE	3.4±0.2	3±0.6	5.1±0.3	0.3±0.1	8.9±0.5	5.6±0.5	0.4±0.1

PEEP= positive end expiratory pressure; V_{max} = maximum rate of metabolism; Cl=clearance. * calculated based on adjusted total phenytoin concentrations (dphET) at each sampling.

PEEP was not associated with a significant alteration in APACHEII scores (19.2±1.1 versus 20.9±1.5, p=0.238). In addition no significant correlation was observed between calculated V_{max} and Cl of phenytoin and APACHE II scores at sampling times (spearman's ρ =0.066, p=0.782; spearman's ρ =-0.037, p=0.876; respectively.)

DISCUSSION

Our data indicated a wide range of variability (2.6-32.5 mg/l in dphET) that was most similar to findings of Mlynarek (28) in a study of 17 neurosurgical patients (6-34 mg/l) in which, most patients had non-traumatic brain injury. According to APACHE II scores in table 2, patients of this study have had a rapid change in physiological conditions (range=13-30), which may contribute to a great intraindividual and interindividual variability. Assuming APACHE II as a measure of the severity of the patient physiological conditions and therefore as an indirect measure of organ function, the absence of any significant change in an individual APACHE II score for each patient might be considered as a possible reason for the lack of significant alteration in phenytoin concentrations after PEEP elevation. On the other hand, our data did not show any significant correlation between the pharmacokinetic parameters of phenytoin and APACHE II scores at sampling times. These findings are contradict to the results of a study on pharmacokinetic of amikacin in septic patients which showed a significant correlation between

APACHE II score and V_d of amikacin (p=0.003, r²=0.26) (20). This can be explained by the fact that phenytoin is mainly metabolised in the liver and APACHE II is not an appropriate index of hepatic function.

The results of this study did not show any significant alterations in phenytoin concentration and metabolism which could be attributed to application of PEEP.

As far as we know, no study has described whether hemodynamic response and factors associated with a vital support measures such as positive ventilation could affect serum phenytoin clearance. However, the potential effects of PEEP on pharmacokinetic of high extraction ratio drugs and drugs which are predominantly eliminated through the liver, have been reported in several studies (18). In a study on 5 patients, lidocaine pharmacokinetic before and after weaning from mechanical ventilation was compared and an increase in peak and steady state plasma concentrations and a decrease in clearance of patients who were subjected to mechanical ventilation was found (19). The volume of distribution however did not change significantly. Also through studying the relationship between hemodynamic measures and pharmacokinetic behaviors of amikacin in 30 critically ill septic patients, it has been demonstrated a poor but significant relationship between application of PEEP mode (about 10±6 cm H₂O) and both V_d and clearance (20). The influence of controlled mechanical ventilation on the pharmacokinetic

profile of gentamicin in 23 patients after elective open-heart surgery has been also reported (29). The results suggested that controlled mechanical ventilation leads to an increase in gentamicin V_d through a decrease in urine volume and negative water clearance.

The lack of the influence of PEEP on disposition of phenytoin which was detected in this study may seem to be odd, however there are some explanations.

First, it is well established that PEEP can cause deleterious hemodynamic effects. The most obvious of these effects is a decrease in cardiac output which is induced by two mechanisms: 1) increase in intrathoracic pressure, which results in a decrease in venous return to the heart (30) and 2) at higher levels of PEEP, a shift of the interventricular septum, which results in a reduced stroke volume (12,31). Consequently, it is well known that application of PEEP causes a reduction in mean arterial pressure (MAP), central venous pressure (CVP) as well as decrease in hepatic, and renal blood flow (32).

However, as demonstrated by several experimental studies the deleterious hemodynamic effects may be minimized by a reduction of airway pressure and may be alleviated at least in part by inotropic agents or fluid administration (17,33,34).

In the present study patients were appropriately hydrated and were on drugs which are known to cause an increase in blood pressure and cardiac output (e.g. dopamine and dobutamine) as required. This is evidenced by the absence of any significant reduction in either MAP ($p=0.919$), or CVP ($p=0.721$) after application of PEEP of 5-10 cm H₂O.

Secondly, we had some clinical limitations for intervening higher levels of PEEP (i.e., ≤ 15 cm H₂O), which probably could have more profound effects on splanchnic blood flow and consequently drug metabolism.

It is well established that there is a positive correlation between the PEEP level and the amount of splanchnic blood flow reduction (35,36). This means that application of higher levels of PEEP are associated with more profound decrease in splanchnic blood flow which could not be reversed by fluid administration and inotropic supports. This is due to the fact that the decrease in venous return could be overcome by fluid administration, but the shift of interventricular septum which occurs in higher levels of PEEP seems to be resistant to therapy (31,33). For example, it has been reported that dopamine reverses the decreased portal venous blood flow that occurs in a canine model of acute lung injury in which 10-cm H₂O pressure

PEEP is added (34). However, in a rat model of acute lung injury, it has been shown that under increasing levels of PEEP (from 0 up to 20 cm H₂O), administration of higher doses of dopamine and dobutamine (12.5 versus 2.5 $\mu\text{g}/\text{kg}/\text{min}$) could only partially correct the cardiac output depression. However, significant declines in cardiac output at ≥ 10 cm H₂O of PEEP were still sustained (37).

In another study for evaluation of the pharmacokinetic behavior of aminophylline under positive ventilation in acute lung injury patients, in which higher levels of PEEP (10-15 cm H₂O) than those that were used in present study (5-9 cm H₂O) were employed, a significant reduction in V_d and clearance in higher PEEP group versus levels of 5-9 cm H₂O was observed (21).

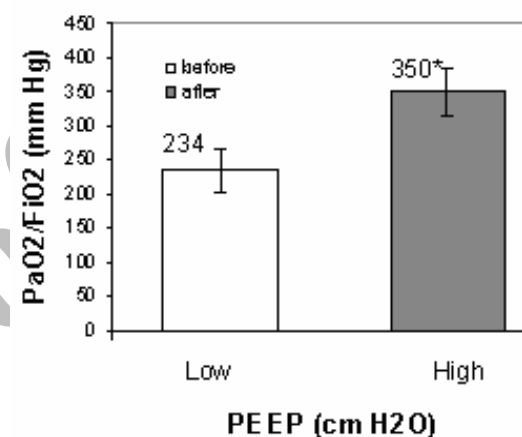


Figure 1. Comparison of PaO₂/FiO₂ ratios before and after PEEP elevation.

PEEP=positive end expiratory pressure; Low= peep levels of 0-5 cm H₂O; High=peep levels of 5-10 cm H₂O * $p<0.05$

Finally, there are some evidences that PEEP induced liver hypoperfusion and hypoxia could be compensated by some mechanisms. As it has been demonstrated, decreased organ perfusion due to PEEP effect may be compensated by an increased oxygen extraction if pulmonary gas exchange is sufficient (34). In another word, splanchnic oxygen consumption may remain unchanged due to an increase in oxygen extraction. The observation of a significant improvement in PaO₂/FiO₂ ratios from 234 \pm 33 to 350 \pm 36 ($p=0.023$) after application of PEEP in the present study potentiates this assumption (Figure 1).

Nevertheless, to establish whether the correction or compensation of the deleterious hemodynamic and oxygenating effects of PEEP is responsible for the observed configurations, requires a simultaneous advanced evaluation of more specific hemodynamic profiles such as cardiac output, portal, hepatic or mesenteric blood flow, as well

as measurement of the hepatic oxygenation. Although, the impact of concomitant medications on metabolism could not be specifically evaluated because of the small sample size, the contribution of drug interactions to the observed variability also should not be ignored.

In this study the phenytoin free level was also calculated according to Sheiner-Tozer equation. On the basis of data shown in table 2, levels of dphEF in 7 cases were subtherapeutic (considering 0.1-0.2 mg/l as therapeutic range). However, except for the patient No 9 in whom phenobarbital was added due to uncontrolled seizures, there were no reports of convulsive seizures during the study. Because EEG monitoring was not available in ICU setting, the possibility of ongoing nonconvulsive seizures dose exist. As a result whether these levels of phenytoin are adequate for making the patients of this population free of seizure is not clear and requires larger sample size, well controlled conditions and direct measurement of free concentration of phenytoin to make the rational decision.

In conclusion, no inhibitory effects for these

levels of PEEP were found to increase concentration and to suppress V_{max} and Cl . Although therapeutic drug monitoring is highly recommended, it seems that application of PEEP in those levels which are usually used to optimize oxygenation in brain-injured patients may not require to adjust doses.

The variabilities observed in the results and the absence of PEEP effect on our data can be explained partially by the possible effects of fluid therapy and medications such as dopamine and dobutamine which reverse the hemodynamic compromise due to positive ventilation.

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