INDUCED HYPOCAPNIA IS EFFECTIVE IN TREATING PULMONARY HYPERTENSION FOLLOWING MITRAL VALVE REPLACEMENT

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Abstract

Background: Mitral valve stenosis is often associated with increased pulmonary vascular resistance resulting in pulmonary hypertension, which may lead to or exacerbate right heart dysfunction. Hypocapnia is a known pulmonary vasodilator. The purpose of this study was to evaluate whether induced hypocapnia is an effective treatment for pulmonary hypertension following elective mitral valve replacement in adults.

Methods: In a prospective, crossover controlled trial, 8 adult patients with mitral stenosis were studied in the intensive care unit following elective mitral valve replacement. Hypocapnia was induced by removal of previously added dead space. Normocapnic (baseline), hypocapnic and recovery hemodynamic parameters including cardiac output, pulmonary vascular resistance, pulmonary artery pressure and systemic oxygen delivery and consumption were recorded.

Results: Moderate hypocapnia (an end-tidal carbon dioxide concentration reduced to 28 ± 5 mmHg) resulted in decreases in pulmonary vascular resistance and mean pulmonary artery pressure of 33% and 25%, respectively. Hypocapnia had no other hemodynamic or respiratory effects. The changes in pulmonary vascular resistance and mean pulmonary artery pressure were reversible.

Conclusion: Moderate hypocapnia was effective in decreasing pulmonary vascular tone in adults following mitral valve replacement. The application of this maneuver in the immediate postoperative period may provide a bridge until pulmonary vascular tone begins to normalize following surgery.

Introduction

Mitral stenosis is one of the most common diseases of the atrio-ventricular valves. Although rheumatic fever, the most frequent cause of mitral stenosis, has been largely eliminated in the West, it remains a major health problem in Third World countries[1]. Less frequent causes of mitral valve stenosis are congenital heart disease, systemic lupus erythematosus, atrial myxoma, malignant carcinoid, and bacterial endocarditis[1]. Treatment of symptomatic mitral stenosis often involves mitral valve repair or replacement[1].

Mitral valve stenosis is often associated with pulmonary hypertension. Traditionally, pulmonary

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hypertension has been treated with intravenous vasodilators, including sodium nitroprusside[2], nitroglycerin[3,4], prostaglandin E1[5], isoproterenol[6], amrinone and milrinone[7], and diazoxide[8]. However, the use of these drugs is limited by a lack of pulmonary vascular selectivity, and, in some cases, by a prolonged elimination half-life[4,9]. More recently, nitric oxide gas and other inhaled vasodilators[2,3,10-19] have been popularized because their use results in selective pulmonary effects and limited systemic effects. However, the use of nitric oxide gas is expensive, requires a special delivery system, and results in rebound pulmonary hypertension following discontinuation[19]. A recent study has demonstrated that inhalation of milrinone, a drug that may be free of these aforementioned shortcomings, attenuated pulmonary hypertension in a rat model of congestive heart failure[20]. Although these findings are promising, their applicability to the patient with pulmonary hypertension following mitral valve repair remains to be determined.

It is well established that the partial pressure of carbon dioxide ($PaCO_2$) is an important physiologic determinant of pulmonary vascular tone[21]. Previous findings in laboratory animals[22,23], and humans[12,24-26] have shown that hypocapnia can cause significant pulmonary vasodilating actions. Furthermore, Drummond and colleagues[27] demonstrated that reducing $PaCO_2$ produced a consistent and reproducible reduction in pulmonary vascular resistance in infants with pulmonary hypertension. Whether this intervention is also effective in adults is unknown and requires investigation. The current study tested the hypothesis that moderate hypocapnia can be an effective maneuver for decreasing pulmonary vascular resistance in adult patients undergoing mitral valve surgery.

Methods

After approval by the Illinois Masonic Medical Center Institutional Review Board, written and signed informed consent was obtained from 21 patients with severe mitral valve stenosis, as defined by a mitral valve area smaller than 1 cm^2 based on echocardiography and cardiac catheterization, scheduled for elective mitral valve replacement at Illinois Masonic Medical Center. Inclusion criteria were age over 18 years, and a preoperative pulmonary vascular resistance greater than 200 $dyn \bullet s \bullet cm^{-5}$ (normal range 50 to 150 $dyn \bullet s \bullet cm^{-5}$). Exclusion criteria were a history of lung disease (evidence of chronic obstructive lung disease or end-stage emphysema), diagnosis of both mitral valve stenosis and severe mitral regurgitation, multiple valve replacements, combined mitral valve and coronary artery bypass procedures, mitral valve repair, and a preoperative requirement for intravenous vasodilators or inotropic drugs or a ventricular assist device. We cannot preclude the possibility that some patients that were allowed to participate in the study had a mild degree of mitral regurgitation.

Upon arrival to the operating room, standard monitors, including 5-lead electrocardiogram, noninvasive arterial blood pressure, and pulse oximetry, were applied. A catheter was placed in a radial artery for continuous measurement of arterial blood pressure and blood sampling. A 7F or 7.5F balloon-tipped thermodilution catheter was placed in the right internal jugular vein and positioned in the pulmonary artery for monitoring of pulmonary artery and pulmonary capillary wedge pressures, measurement of cardiac output, and sampling mixed venous blood. Preoperative hemodynamic data and arterial and mixed venous blood gases were obtained immediately prior to induction of anesthesia. Anesthesia was induced and maintained with fentanyl (100 mcg/kg) supplemented with isoflurane (1%–2% in oxygen). Cardiopulmonary bypass was instituted using crystalloid priming. Muscle relaxation was induced and maintained with vecuronium. Core temperature was continuously monitored via a nasopharyngeal probe. Inspired and end-tidal carbon dioxide

were continuously monitored. The effects of all anesthetic drugs were allowed to reverse spontaneously.

After the completion of mitral valve replacement, an additional dose of vecuronium (0.5 mg/kg) was administered and the patient was transferred to the surgical intensive care unit. Postoperative mechanical ventilation was maintained with the use of synchronized intermittent mandatory ventilation mode with a tidal volume of 10 mL/kg, a rate of 10 breaths/min, an inspired oxygen fraction of 0.6 to 1.0, and a positive end-expiratory pressure of 5 cm H_2O. The ventilator (Bennett MA1, Puritan Bennett, USA) was initially adjusted to obtain a value for $PaCO_2$ between 37 and 44 mmHg.

The prospective, crossover, controlled study protocol commenced after the following criteria were met: 1) at least two hours had elapsed since arrival of the patient in the surgical intensive care unit, 2) the patient had exhibited no spontaneous ventilatory efforts, and 3) two hours had elapsed following discontinuation of any cardioactive drug. The inspired oxygen fraction was then increased to 1.0. A technique of "constant volume hyperventilation", was employed to induce hypocapnia with minimal changes in lung mechanics[28, 29]. This was accomplished by initially increasing tidal volume by 200 mL while adding 200 mL mechanical dead space distal to the Y-piece, thus yielding a baseline normocapnic condition. A 30-min equilibration period was allowed, after which hemodynamic measurements and blood gases/pH were obtained. Moderate hypocapnia, defined as a $PaCO_2$ between 30 and 35 mmHg, was then instituted by removal of the dead space without changing the ventilator settings. End-tidal carbon dioxide concentration was continuously monitored and used as an index of alveolar carbon dioxide concentration. After 30 minutes of hypocapnia, blood gases/pH and the hemodynamic measurements were repeated. Thereafter, the dead space tubing was returned to the breathing circuit in order to restore normocapnia. Thirty minutes later, a set of recovery values of measured and calculated hemodynamic and respiratory parameters was obtained (Table 1). Following conclusion of the study protocol, the dead space tubing was removed and the tidal volume and inspired oxygen fraction were returned to the pre-experimental settings, i.e., tidal volume of 10 to 15 ml/kg, rate of 10 breaths/min, inspired oxygen fraction of 0.6 to 1.0, and positive end-expiratory pressure of 5 cm H_2O.

Table 1

Measured and calculated parameters recorded at each measurement period

Parameters	Measured or Calculated	Equation for Calculated Parameters
Heart Rate (beats/min)	Measured	
Mean Arterial Blood Pressure (mmHg)	Measured	
Stroke Volume (cc)	Calculated	CO/HR
Cardiac Output (L/min)	Measured	
Cardiac Index ($L \bullet min^{-1} \bullet m^{-2}$)	Calculated	CO/BSA
Mean Central Venous Pressure (cm H_2O)	Measured	
Mean Pulmonary Artery Pressure (mmHg)	Measured	
Pulmonary Capillary Wedge Pressure (mmHg)	Measured	

Airway Pressure (cm H_20)	Measured	
Pulmonary Vascular Resistance (dyn•s•cm^{-5})	Calculated	80 x (MPAP - PCWP)/CO
Systemic Vascular Resistance (dyn•s•cm^{-5})	Calculated	80 x (MAP - CVP)/CO
Arterial Blood Gases/pH	Measured	
Hemoglobin (gm/dL)	Measured	
Mixed Venous Blood Gases/pH	Measured	
End-tidal carbon dioxide tension (mmHg)	Measured	
Skin & blood temperature (ºC)	Measured	
Inspired oxygen fraction	Measured	
Arterial Oxygen Saturation (%)	Measured	
Mixed Venous Oxygen Saturation (%)	Measured	
Whole Body Oxygen Consumption (mL O_2/min)	Calculated	CO/(150 - [$PaCO_2$ x 1.25] - PaO_2)
Oxygen Delivery (mL O_2/100 mL)	Calculated	10 x [Hgb x 1.36 x SaO_2] + [0.0031 x PaO_2]/CO

Statistical Analysis

Statistical analysis was performed using SPSS version 15.0 (SPSS, Chicago, IL). A repeated measures one-way analysis of variance and the least significance difference tests were employed to detect significant differences in continuous variables between the time periods. Statistical significance was accepted when $p < 0.05$. All values are presented as mean ± standard deviation (SD).

Results

Following induction of anesthesia but prior to the institution of cardiopulmonary bypass, eleven patients with pulmonary vascular resistance greater than 200 dyn•s•cm^{-5} were considered eligible for continued participation in the study (Fig. 1 and Table 2). Noteworthy are the values for pulmonary vascular resistance and mean pulmonary artery pressure of 300 ± 78 dyn•s•cm^{-5} and 27 ± 7 mmHg, respectively. The number of eligible subjects was further reduced following surgery when 2 patients required prolonged intravenous infusion of vasopressors or vasodilators and one patient exhibited inspiratory efforts in the postoperative period. Data analysis was performed on the remaining eight patients (3 males and 5 females), who satisfied the study criteria (Fig. 1).

Fig. 1

Flow diagram illustrating subject recruitment and disqualification because of application of exclusion criteria. The study protocol was completed in 8 of the 21 subjects who were originally enrolled.

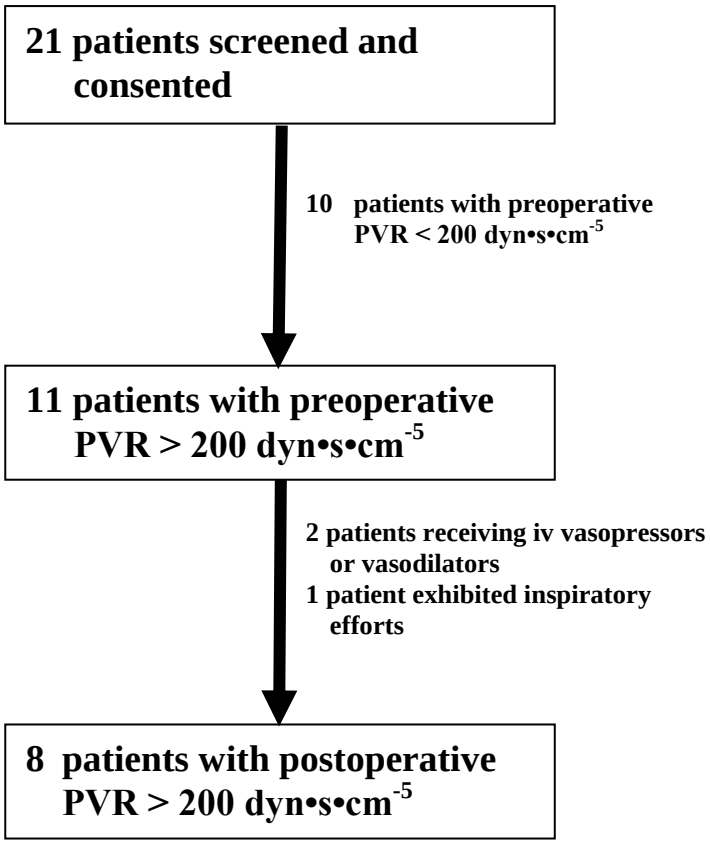


Table 2

Measured and calculated parameters recorded prior to institution of cardiopulmonary bypass

Measured/Calculated Parameter	Mean ± Standard Deviation
Cardiac Output (L/min)	4.0 ± 1.0
Cardiac Index ($L \cdot min^{-1} \cdot m^{-2}$)	2.3 ± 0.6
Heart Rate (beats/min)	78 ± 13
Mean Arterial Pressure (mmHg)	86 ± 8
Central Venous Pressure ($cm\ H_2O$)	12 ± 2
Mean Pulmonary Artery Pressure (mmHg)	27 ± 7
Pulmonary Capillary Wedge Pressure (mmHg)	14 ± 5
Stroke Volume (mL)	52 ± 14
Pulmonary Vascular Resistance ($dyn \cdot s \cdot cm^{-5}$)	300 ± 78
Systemic Vascular Resistance ($dyn \cdot s \cdot cm^{-5}$)	1446 ± 398
Intrapulmonary Shunt (%)	11.3 ± .8
Alveolar-to-Arterial Oxygen Difference (mmHg)	231.0 ± 90.9
Arterial pH	7.41 ± .06
Arterial Carbon Dioxide Tension (mmHg)	39 ± 3
Arterial Oxygen Tension (mmHg)	375 ± 121
Tidal Volume (cc)	813 ± 63
Peak Airway Pressure ($cm\ H_2O$)	31 ± 1
End-tidal Carbon Dioxide Tension (mmHg)	40 ± 3
Respiratory Rate (breaths/min)	10 ± 1
Hemoglobin (gm/dL)	12.8 ± 1.1

Data are mean ± the standard deviation.

Tables 3 and 4 present the effects of induced hypocapnia on pulmonary vascular resistance, mean pulmonary artery pressure, and associated parameters. A reduction in end-tidal carbon dioxide from 39 ± 8 to 28 ± 5 mmHg and the attendant reduction in $PaCO_2$ from 42 ± 6 to 33 ± 4 mmHg and increases in both arterial and venous pH from 7.38 ± 0.07 and 7.33 ± 0.6 to 7.47 ± 0.06 and 7.40 ± 0.6, respectively, were associated with decreases in mean pulmonary vascular resistance and mean pulmonary artery pressure of 33% and 25%, respectively (Tables 3 and 4 and Figure 2). Other hemodynamic and oxygen supply/demand parameters were not affected. The decreases in pulmonary vascular resistance and mean pulmonary artery pressure associated with hypocapnia returned to the normocapnic values during recovery (Tables 3 and 4 and Fig. 2).

Table 3

Measured or calculated hemodynamic parameters recorded at normocapnia, induced hypocapnia, and after recovery (normocapnia)

Measured/Calculated Parameter	**Normocapnia**	**Hypocapnia**	**Recovery (normocapnia)**	***p*-value**

Cardiac Output (L/min)	4.5 ± 0.8	4.4 ± 1.0	4.6 ± 0.9	0.692
Cardiac Index ($L•min^{-1}•m^{-2}$)	2.7 ± 0.5	2.7 ± 0.6	2.7 ± 0.5	0.577
Mean Pulmonary Artery Pressure (mmHg)	28 ± 6	21 ± 6*	29 ± 5	0.049
Pulmonary Vascular Resistance ($dyn•s•cm^{-5}$)	246 ± 117	165 ± 80*	256 ± 122	0.044
Heart Rate (beats/min)	77 ± 15	77 ± 14	74 ± 13	0.943
Mean Arterial Pressure (mmHg)	85 ± 12	81 ± 9	80 ± 10	0.551
Central Venous Pressure ($cm\ H_2O$)	11 ± 3	12 ± 4	11 ± 3	0.890
Pulmonary Capillary Wedge Pressure (mmHg)	15 ± 4	16 ± 5	15 ± 5	0.691
Systemic Vascular Resistance ($dyn•s•cm^{-5}$)	1347 ± 305	1283 ± 283	1237 ± 234	0.601

* Statistical significance from any other period ($p < 0.05$)

Data are mean ± the standard deviation.

Table 4

Measured or calculated respiratory parameters recorded at normocapnia, induced hypocapnia, and after recovery (normocapnia).

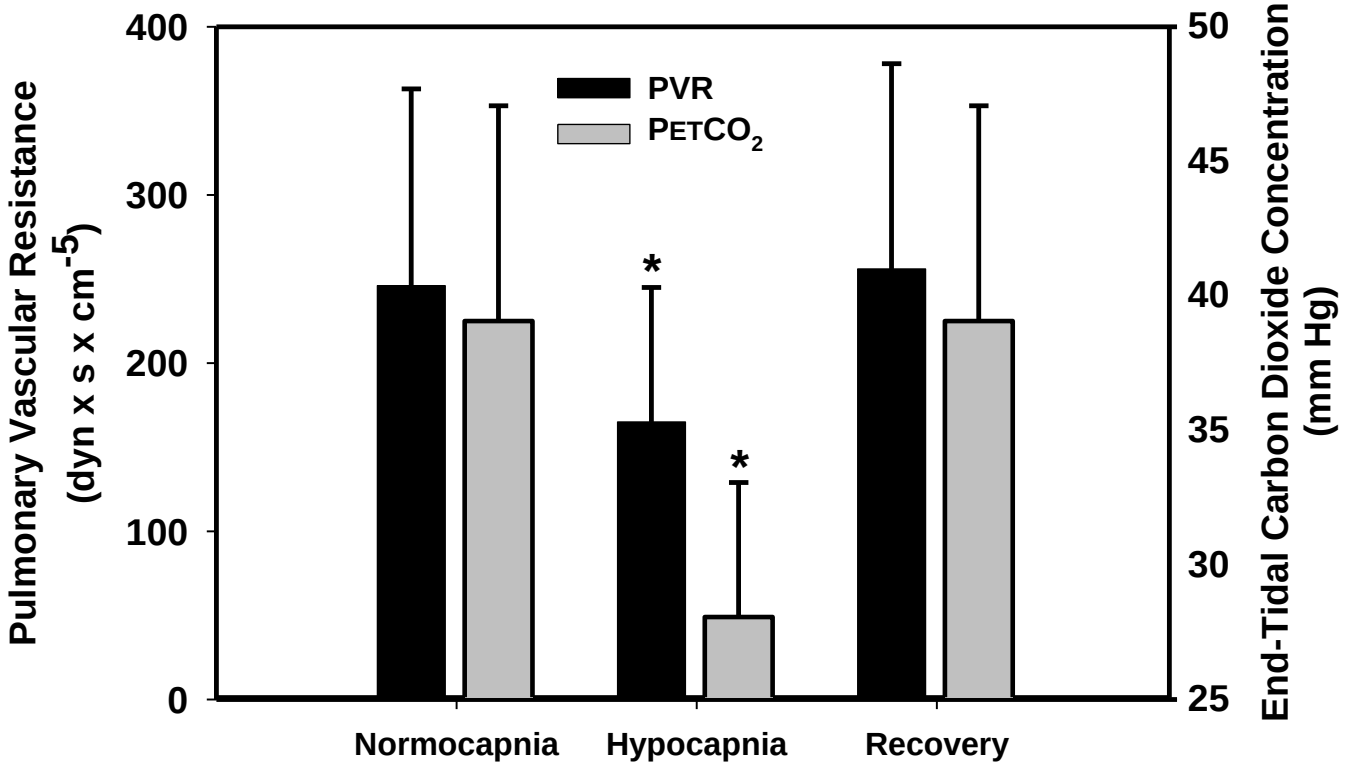
Measured/Calculated Parameter	**Normocapnia**	**Hypocapnia**	**Recovery (normocapnia)**	***p*-value**
End-tidal Carbon Dioxide Tension (mmHg)	39 ± 8	28 ± 5*	39 ± 8	0.011
Airway Pressure ($cm\ H_2O$)	35.7 ± 6.6	36.7 ± 6.9	35.1 ± 4.7	0.511
Arterial pH	7.38 ± 0.07	7.47 ± 0.06*	7.38 ± 0.07	0.013
Arterial Carbon Dioxide Tension (mmHg)	42 ± 6	33 ± 4*	43 ± 6	<0.001
Arterial Oxygen Tension (mmHg)	328 ± 109	307 ± 101	342 ± 101	0.716
Mixed Venous pH	7.32 ± 0.06	7.40 ± 0.06*	7.32 ± 0.07	0.047
Mixed Venous Carbon Dioxide Tension (mmHg)	50.9 ± 5.3	41.4 ± 2.5*	49.03 ± 4.6	0.001
Mixed Venous Oxygen Tension (mmHg)	46.3 ± 11.7	39.5 ± 9.4	45.6 ± 11.1	0.443
Systemic Oxygen Consumption ($mL•min^{-1}•m^{-2}$)	598 3 ± 116.7	592 ± 134.9	606.0 ± 116.6	0.969
Whole body Oxygen Delivery ($mL•min^{-1}•m^{-2}$)	220.6 ± 171.9	246.2 ± 154.3	234.9 ± 155.7	0.938

* Statistical significance from any other period ($p < 0.05$)

Data are mean ± the standard deviation.

Fig. 2

Pulmonary vascular resistance (PVR) and end-tidal carbon dioxide concentration ($PETCO_2$) obtained during normocapnia, induced hypocapnia and following return to normocapnia (recovery). Data presented as mean ± standard deviation.



* denotes statistically significant difference from all other time periods ($p < 0.05$).

There were no adverse events or complications associated with the conduct of this study. All patients' tracheas were extubated within two to six hours after completion of the study protocol.

Discussion

Increased pulmonary vascular resistance leading to pulmonary hypertension and right ventricular failure is frequently observed in patients with mitral valve stenosis. These conditions can often persist immediately following mitral valve surgery and can complicate management in the postoperative period[30]. Pathophysiologic mechanisms contributing to increased pulmonary vascular resistance and pulmonary hypertension include: 1) an increased left atrial pressure transmitted retrogradely into the pulmonary arterial circulation, 2) vascular remodeling of the pulmonary vasculature in response to chronic obstruction of pulmonary venous drainage, and 3) pulmonary vasoconstriction[30,31]. Although mitral valve replacement has been frequently demonstrated to eliminate the increased left atrial pressure[31], the other contributing factors persist following mitral valve surgery. Vascular remodeling is a "fixed" component[3] and is not responsive to perioperative interventions. On the other hand, pulmonary vasoconstriction is a "reactive" component that can be manipulated in the

intraoperative and immediate postoperative periods[3,26,30,31].

It is well established that hypocapnia can cause changes in the distribution of cardiac output and regional blood flow[23]. In the systemic circulation, the change in blood flow is the result of the balance between the vasodilating effect of an attenuated sympathetic vasoconstrictor nerve discharge secondary to reduced activation of the arterial chemoreceptors, e.g., the carotid bodies, and the local ability of hypocapnic alkalosis to directly cause an increase in vascular smooth muscle tone, i.e., vasoconstriction[32,33]. Unlike the systemic circulation, hypocapnia has a vasodilating effect in the pulmonary circulation[34,35]. This unique behavior is attributable to the ability of hypocapnic alkalosis to cause an increase in production of prostacyclin (a powerful vasodilator) in the pulmonary endothelial cells, while having no effect on prostacyclin levels in systemic endothelial cells[36]. Another fundamental difference between the pulmonary circulation and the systemic circulation relates to the local hypocapnic stimulus controlling vascular tone. Because the alveolar capillaries constitute an air-blood exchange interface, a reduction in alveolar PCO_2 (P_AO_2) is the primary stimulus for pulmonary vasodilation, although a reduction in mixed venous PCO_2 ($P\bar{v}O_2$) may also play a role[35].

As reviewed by Laffey and Kavanagh[37], hypocapnia can have an impact on the balance between cerebral oxygen supply and demand. This is a major concern when hypocapnia is induced deliberately, is accidental or disease related. Hypocapnia can reduce oxygen supply by causing cerebral vasoconstriction[23,29] and a leftward shift in the oxyhemoglobin dissociation curve (which can impair unloading of oxygen at the tissue level)[21].

A mild form of hypocapnia ($P_{ET}CO_2$ of 28 ± 5 mmHg) was induced in the present study to minimize its effects in the brain. The findings demonstrated that hypocapnia of this degree was capable of producing pronounced decreases in mean pulmonary artery pressure and pulmonary vascular resistance. In the absence of cerebral oximetry we had no direct measurement of its effect on cerebral oxygenation. However, previous studies have shown that the decrease in PCO_2 that we evaluated causes an approximate 20% reduction in cerebral blood flow 38. It is well established that the brain has a considerable oxygen extraction reserve which should be capable of offsetting this decrease in cerebral blood flow, despite an impairment to oxygen unloading[39]. Moreover, previous work in our laboratory has demonstrated the cerebral vasconstrictor effect of hypocapnia is obtunded during hemodilution[29], which would have an ameliorating influence on the hypocapnia-induced decreases in cerebral blood flow in the subjects of this study.

The advantages of induced hypocapnia were that it was easily applied in the mechanically ventilated patient, required no added expense, had an immediate effect, and showed no degradation. In addition, induced hypocapnia was easily reversed, was not associated with any significant systemic hemodynamic effects, and showed no rebound effects in the pulmonary circulation.

Several limitations of the study warrant address. First, the present study only evaluated the effect of hypocapnia in patients with pulmonary hypertension from mitral valve stenosis. Thus, extrapolation of the findings to patients with pulmonary hypertension from other causes would be inappropriate. Second, a standard 30 min of duration of hypocapnia was evaluated. It is not known whether the reduction in pulmonary vascular resistance would persist for longer periods of hypocapnia. Third, a single moderate level of hypocapnia was examined. It remains to be determined whether the decrease in pulmonary vascular resistance is a threshold response or whether it will vary as a function of the degree of hypocapnia. Finally, the study would have benefited from transesophogeal echocardographic measurements to evaluate whether the hypocapnia-induced decreases in pulmonary artery pressure had a positive impact on the right ventricle, e.g., on right ventricular size, tricuspid regurgitation, or right ventricular strain.

In conclusion, the current findings provide preliminary evidence that moderate hypocapnia may be an effective and easily administered technique to reduce pulmonary vascular resistance in patients undergoing mitral valve surgery. In this role, the technique would provide a bridge until pulmonary vascular tone begins to normalize following surgery. Induced hypocapnia may have applications as an adjunct to other treatments for pulmonary hypertension.

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