Pulmonary Vascular Responses to Moderate Changes in $P_{aCO_2}$ after Cardiopulmonary Bypass

M. Salmenperä, M.D.* and J. Heinonen, M.D.*

Clinical observation by the authors suggests that small changes in $P_{aCO_2}$ cause significant alterations in pulmonary hemodynamics after cardiac surgery. To examine this, the authors induced moderate ventilatory hypocarbia ($P_{aCO_2} = 30.7 \pm 0.4$ mmHg, mean $\pm$ SD) in eight patients early after coronary artery bypass surgery. Normocarbia ($40.6 \pm 0.5$ mmHg) and hypercarbia ($51.5 \pm 0.5$ mmHg) were then induced by adding CO$_2$ to the inspired gas. Standard hemodynamic measurements were performed at each stage. In four of the patients, CO$_2$ exposure was subsequently withdrawn in reversed order. There were no clinically significant changes in systemic hemodynamics. Despite unchanged pulmonary blood flow, in all patients pulmonary artery pressure increased with increasing $P_{aCO_2}$. An almost two-fold and three-fold increase was observed in the mean pulmonary vascular resistance (PVR) and pulmonary diastolic gradient (pulmonary artery diastolic pressure–pulmonary capillary wedge pressure), respectively, when $P_{aCO_2}$ was changed from hypocarbia to hypercarbia. The changes in the pulmonary diastolic gradient correlated ($r = 0.77$, $P < 0.001$) with the changes in the PVR. The pulmonary vasoconstrictor response was reversible with CO$_2$ washout. Avoidance of even moderate hypocarbia, therefore, seems advisable in the early postperfusion stage because of a further potential impedance to right ventricular ejection. Frequent measurement of pulmonary diastolic pressure gradient provides a useful method of rapid estimation of the resistance to flow in the pulmonary vascular bed. (Key words: Acid–base equilibrium; respiratory acidosis; respiratory alkalosis. Carbon dioxide; hypercarbia; hypocarbia. Lung; blood flow; vascular resistance; shunting.)

INCREASE OF carbon dioxide tension in arterial blood depresses myogenic tonic activity in precapillary resistance vessels of the systemic circulation. In contrast, hypocarbia leads to pulmonary vasoconstriction in experimental animals. Corresponding data in normal humans are meager and controversial. Cardiopulmonary bypass (CPBP) has been shown to cause a reversible increase of pulmonary vascular resistance (PVR) in humans, and pulmonary circulation might be particularly susceptible to further vasoconstrictor influences in the postbypass period. We have witnessed several occasions of hemodynamic instability after CPBP with an increasing pulmonary artery pressure as the main feature. These episodes were associated with hypercarbia and were reversed by increasing the ventilation. Because slight deviations from normocarbia are a common occurrence after cardiac surgery, we decided to study the extent to which such changes modify the resistance variables of the pulmonary circulation in patients recovering from coronary artery bypass grafting (CABG).

Methods

Eight patients recovering from CABG were studied according to the study protocol approved by the Ethical Committee of the Department. The patients were considered for the study if they had no or only moderate impairment of left ventricular function as shown by an ejection fraction of greater than 0.40 and a negative history of congestive heart failure. They were all receiving a beta-adrenergic blocking drug and a long-acting nitrate. Six of the patients also used a calcium-entry blocker. These antianginal medications were continued until surgery. The patients underwent standard coronary artery bypasses with internal mammary artery and/or saphenous vein grafts. Anesthesia was achieved with fentanyl 75 $\mu$g kg$^{-1}$ and ventilation with oxygen in air (fractional inspired O$_2$ concentration [FIO$_2$] 0.5). Details of the anesthesia technique and the perfusion procedure have been reported earlier. Myocardial revascularization was assessed as complete in all of the patients, and they had been weaned from CPBP without inotropic or vasodilatory drugs. The characteristics of the study group are given in table 1.

The study interventions began about 2 h after the end of CPBP when at least 30 min had elapsed from the end of surgery. The patients were still unconscious and artificially ventilated (Servo 900 B* ventilator). Ventilation was increased to keep the respiratory rate constant at 12 breaths min$^{-1}$ and changing the tidal volume to about 12 ml kg$^{-1}$ to reach a $P_{aCO_2}$ level of 27.5–32.5 mmHg. After a stabilization period of 10 min, blood samples were drawn, and the hemodynamic measurements performed. CO$_2$ was then added to the inspired gas to reach first a $P_{aCO_2}$ level of 37.5–42.5 mmHg and thereafter of 47.5–52.5 mmHg. The ventilation was kept constant, and oxygen was added to keep FIO$_2$ at 0.50 as measured by a polarographic oxygen analyzer. At both levels of increased $P_{aCO_2}$, the study measurements were obtained after a stabilization period of 10 min. In four of the patients, CO$_2$ was withdrawn from the inspired gas in reversed order to assess the reversibility of the hemodynamic changes.

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Received from The Department of Anesthesia, Helsinki University Central Hospital, Haartmaninkatu 4, SF-00290 Helsinki 29, Finland. Accepted for publication October 21, 1985. Supported by a grant from the Paulo Foundation. Presented in part at the 6th Annual Meeting of the Society of Cardiovascular Anesthesiologists, Boston, 1984. Address reprint requests to Dr. Salmenperä.
Table 1. Patient Characteristics (mean ± SD and range of eight patients presented)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Results</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>52.9 ± 0.8 (33–69)</td>
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<tr>
<td>Body surface area (m²)</td>
<td>1.93 ± 0.11 (1.81–2.10)</td>
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<tr>
<td>Ejection fraction</td>
<td>0.51 ± 0.10 (0.42–0.72)</td>
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<td>Duration of aortic crossclamp (min)</td>
<td>64.8 ± 13.5 (45–84)</td>
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<tr>
<td>Duration of cardiopulmonary bypass (min)</td>
<td>97.3 ± 14.7 (74–118)</td>
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Mean arterial pressure (MAP) was recorded through an indwelling 20-g cannula in the radial artery. Mean pulmonary artery pressure (MAP), diastolic pulmonary artery pressure (DPAP), pulmonary capillary wedge pressure (PCWP), and central venous pressure (CVP) were recorded with the aid of a triple-lumen thermodilution pulmonary artery catheter. All the pressures were obtained using appropriate transducers zeroed to the midaxillary level and recorded with an ink-jet recorder. Actual pressure curves at end expiration were used to calculate the DPAP–PCWP gradient. All the other pressures were obtained using electronic integration. Cardiac output (CO) was measured in triplicate by thermal dilution using 10 ml of 0.9% saline at room temperature. Cardiac index (CI), systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were calculated using standard formulae. For the determination of intrapulmonary shunt (Qs/QT), arterial and mixed venous blood samples were drawn, and hemoglobin content and blood gas tensions were analyzed. Qs/QT was calculated as described by Ruiz et al.8

The values obtained at different PacO₂ levels were compared using analysis of variance (ANOVA) with repeated measures design. In case of significance (P < 0.05)

Table 2. pH and PacO₂ in Arterial and Mixed Venous Blood (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>PacO₂ (mmHg)</th>
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<tr>
<td></td>
<td>30.7 ± 0.4</td>
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<tr>
<td>pHₐ</td>
<td>7.46 ± 0.03*</td>
</tr>
<tr>
<td>pHₓ</td>
<td>7.42 ± 0.03†</td>
</tr>
<tr>
<td>PacO₂ (mmHg)</td>
<td>174.4 ± 36.0</td>
</tr>
<tr>
<td>PacO₂ (mmHg)</td>
<td>59.2 ± 4.3</td>
</tr>
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</table>

* P < 0.01; significant difference versus normocarbia.
† P < 0.001; significant difference versus normocarbia.

After ANOVA, values at hypocarbia and hypercarbia were compared with those at normocarbia using the t test for paired data. Bonferroni’s method was used to correct for multiple comparisons. Simple linear regression analysis was used to assess the correlation between variables.

Results

The PacO₂ levels attained at the measurement stages were 30.7 ± 0.4, 40.0 ± 0.5 and 51.5 ± 0.5 mmHg (means ± SD) during hypocarbia, normocarbia, and hypercarbia, respectively. The corresponding values of pH and PacO₂ in arterial and mixed venous blood are given in table 2.

Systemic Hemodynamics (Table 3)

The only noteworthy significant change was the roughly 9% decrease in mean SVR from normocarbia to hypercarbia.

Pulmonary Hemodynamics (Figs. 1 and 2)

Pulmonary arterial pressure increased consistently with increasing PacO₂ (fig. 1). Because left heart filling pressure and pulmonary blood flow were essentially unchanged (table 2), the resistance variables of the pulmonary circulation, DPAP–PCWP, and PVR, followed closely the trend observed in pulmonary arterial pressure. There was a significant correlation between the changes in DPAP–PCWP and PVR (r = 0.77, P < 0.001), the regression equation being: ΔPVR = 18.92 × (ΔDPAP–PCWP) + 8.11. Qs/QT decreased with increasing PacO₂, the decrease from 9.0% during normocarbia to 7.7% during hypercarbia being statistically significant.

In the four patients studied, changes in pulmonary hemodynamics were reversible when CO₂ challenge was withdrawn. This is shown in the case of PVR in figure 2.
Discussion

Our results indicate that moderate alterations of CO₂ tension, such as occur commonly in clinical situations, significantly modify resistance to blood flow in pulmonary vasculature in patients recovering from CABG. The increase in resistance is completely reversible, disappearing as PaCO₂ is brought back to normocarbic or hypocarbic level. Although the maintenance of normal PaCO₂ is an undisputable goal when caring for patients in the post-bypass period, this aim is not always strictly achieved. While controlled mechanical ventilation often leads to slight hypocarbia in these hypothermic patients, return of consciousness, spontaneous rewarming, and, particularly, shivering all contribute to frequent episodes of respiratory acidosis.⁹

In this study we chose to vary the blood tension of CO₂ by deliberate hyperventilation and subsequent adjustments of the inspired fraction of CO₂. The relatively large tidal volumes used may have contributed to the somewhat higher baseline PVR values in these patients¹⁰ as compared with the values we have reported earlier in a similar group of patients.⁷ Although the addition of CO₂ to the inspired gas permits observations under unchanged intrathoracic ventilatory pressure–volume conditions, this intervention is artificial and, therefore, the results may not be directly applicable to the clinical situations. In our patients, the exposure of the upper airways to constant increased CO₂ concentrations may have activated the CO₂-sensitive receptors in the airways as shown in dog experiments.¹¹ However, the only known effenter activity resulting from the activation of these receptors is an increase of respiratory rate. Bearing in mind the similarity of the responses observed in the present study to those seen occasionally in postoperative cardiac patients (fig. 3), we believe that our study model warrants conclusions as to what is happening in the pulmonary circulation when CO₂ is increased by intrinsic mechanisms.

Most of the studies dealing with circulatory effects of CO₂ focus attention on systemic hemodynamics. Considering the very gradual slope of the decrement of CO with decreasing CO₂ tension (0.5–1.0%/mmHg),¹ it is not

![FIG. 1. Pulmonary vascular responses to graded CO₂ inhalation in eight patients early after coronary artery bypass surgery. HYPO = PaCO₂, 30.7 ± 4 mmHg (mean ± SD); NORMO = PaCO₂, 40.6 ± 5.5; HYPER = PaCO₂, 51.5 ± 5.5. MPAP = mean pulmonary artery pressure. DPAP–PCWP = gradient of diastolic pulmonary artery pressure to pulmonary capillary wedge pressure. PVR = pulmonary vascular resistance. Q̇O₂/Q̇F = intrapulmonary shunt.](image)

![FIG. 2. Pulmonary vascular resistance response to graded CO₂ inhalation (HYPO–NORMO–HYPER) and CO₂ washout (HYPER–NORMO–HYPO) in four patients early after coronary artery bypass surgery.](image)

![FIG. 3. Pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure (PCWP) tracings in a patient about 2 hr after cardiopulmonary bypass. Left tracing = inadvertent hyperventilation. Middle tracing = normoventilation after ventilator adjustments. Right tracing = hyperventilation, unchanged ventilator setting, but the patient is shivering.](image)
surprising that the slight hypocarbia in our patients did not produce any changes in cardiac flow or in the other systemic hemodynamic variables. The response of cardiac output to hypercarbia has been shown to be much steeper (3–5%/mmHg) in ventilated anesthetized patients. This increase is totally mediated by the release of catecholamines from adrenergic nerve endings and the adrenal medulla. The absence of CO response in our postoperative cardiac surgical patients could be related to the increased sympathetic tone in these patients. Perhaps under these conditions the CO₂ increase was too weak a stimulus to amplify this tone further. The nonexistence of the response could in part be related to the residual β-adrenergic blockade in these patients.

The distinct increase in the pulmonary artery pressure with unchanged pulmonary blood flow implies a marked pulmonary vasoconstrictor effect of the increasing PₐCO₂ in our patients. Because we did not study our patients before CPBP, we cannot argue that CPBP had rendered the pulmonary circulation particularly reactive to vasoconstrictor influences. However, previous studies have shown that PVR is increased after CPBP in patients undergoing CABG, and patients with an increased baseline PVR have been reported to show an exaggerated response to a pulmonary vasoconstrictor like nitrous oxide. Although CO₂ inhalation has been shown to increase pulmonary artery pressure in humans with healthy lungs, this has been attributed to be a passive consequence of increased cardiac output. However, a pronounced vasoconstrictor response such as that seen in our patients has been shown to occur in patients with congenital heart disease or chronic obstructive lung disease. In neonates with persistent pulmonary hypertension, induced ventilatory hypocarbia has been recommended as a therapeutic modality to reduce pulmonary artery pressure and right-to-left shunt.

Respiratory acidosis has been shown to enhance hypoxic pulmonary vasoconstriction (HPV) in dogs. On the other hand, a decrease in alveolar and PₐCO₂ is associated with a release of HPV in the same species. In addition, acidosis and hypoxemia seem to interact additively in producing an increase in pulmonary artery pressure in man. Our patients did not have arterial hypoxemia, but obviously an increased HPV may have been present in them after CPBP. It may be assumed that if CO₂ had acted uniformly in all pulmonary vascular segments of our patients, the shunt fraction should have remained unchanged. Because this was not the case, and a decrease in shunt accompanied the increase in PVR, an increase of HPV might have occurred in our patients with the increase in PₐCO₂.

When PVR is increased, the normal diastolic time is insufficient to permit pressure equalization in the pulmonary vascular bed. Consequently, a gradient between DPAP and PCWP will appear. In the absence of tachycardia, this gradient has been considered to be the best index of the resistance to flow in pulmonary circulation. We have previously demonstrated that a clear increase in the pulmonary diastolic gradient appears after CPBP in patients undergoing CABG, and a significant correlation was found between the change in DPAP–PCWP gradient and the change in PVR. This study extends these observations and shows that rapid, chemically induced changes in PVR can easily be detected by monitoring this gradient.

In light of our results, it might seem that, as far as PVR is concerned, moderate hypocarbia is advantageous after cardiac surgery. However, such therapeutic attempts should be made cautiously in light of the potentially serious consequences of hypocarbia.

In conclusion, small increases of PₐCO₂, such as are often encountered after CABG, cause marked increases in resistance to blood flow in the pulmonary vascular bed. These acute increases in right ventricular afterload are likely to be detrimental to patients suffering from right ventricular dysfunction. Meticulous attention should be paid to the detection and prevention of episodes of respiratory acidosis in these patients. We, therefore, recommend continuous monitoring of the end-tidal CO₂ and frequent measurement of pulmonary diastolic pressure gradient in patients early after CPBP.

References

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