Continuous *in-vivo* monitoring of arterial oxygen tension in a patient treated with bleomycin

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Patients receiving bleomycin therapy may develop pulmonary fibrosis. The risk of fibrosis is increased by the administration of general anaesthesia and fatal cases with pulmonary lesions resembling those of "oxygen toxicity" have been reported. The causes are not entirely clear but the enriched inspired oxygen given intraoperatively or postoperatively has been identified as an etiological factor. Optimal intraoperative management thus requires the administration of the lowest inspired oxygen fraction (FiO₂) compatible with adequate oxygenation. To achieve this aim safely, continuous in vivo monitoring of arterial oxygen tension would be preferable to intermittent sampling of blood gases. We report the successful management of a patient undergoing thoracotomy following bleomycin therapy using an intravascular PO₂ sensor to monitor arterial oxygen tension continuously. The uses and limitations of the PO₂ sensor are discussed.

Key words

EQUIPMENT: arterial catheter; HYPOXIA, MEASUREMENT TECHNIQUES: oxygen electrode; TOXICITY: oxygen; BLEOMYCIN: anaesthetic management.

Bleomycin has been used in the preparation of patients with dysgenetic testicular neoplasms¹ and epidermoid oesophageal carcinomas² before surgery. Pulmonary fibrosis is seen in five to 40 per cent of patients treated with bleomycin, and is a major cause of morbidity and mortality. This complication has been especially noted in the elderly, in those treated with large doses of the drug, in those receiving thoracic radiotherapy, and more recently, in patients receiving increased inspired concentrations of oxygen.¹⁻⁵ Goldiner reported the incidence of fatal pulmonary fibrosis in a group of patients treated with bleomycin and found that the mean inspired oxygen fraction (FiO₂) of the survivor group was 0.24 while that of the non-survivor group was 0.39.¹ The arterial oxygenation was monitored by intermittent sampling of blood gases. He concluded that the risk of fatal pulmonary fibrosis can be reduced by decreasing the inspired oxygen concentration intraoperatively as well as postoperatively. Allen⁴ reported two thoracotomies in a patient receiving bleomycin who received an FiO₂ of 0.21-0.25 intraoperatively. During some unexpected bleeding, the FiO₂ was not increased, and an arterial blood gas revealed an arterial oxygen tension of 45 mmHg. The authors "felt obliged to maintain the FiO₂ within known safe limits, and were forced to accept the degree of hypoxia produced by one lung anaesthesia." This case report illustrates a clinical setting not uncommonly encountered. Patients treated with bleomycin frequently present for thoracotomy and one lung anaesthesia, either for oesophageal resection or for removal of a malignant tumour. The risk of pulmonary fibrosis must be balanced against the hazards

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of hypoxaemia during one lung anaesthesia. The goal is to deliver the lowest FiO_2 possible, while avoiding the development of hypoxaemia. Intermittent determination of blood gases as a monitor of oxygenation is plagued by a long lag time between sampling and feedback. We describe the successful intraoperative management of a patient undergoing thoracotomy who was predisposed to the development of pulmonary fibrosis by recent treatment with high doses of bleomycin. We monitored continuously his arterial oxygen tension using an intravascular PO_2 sensor with a Clark-type electrode (Roche, part no. 8803406, supplied by Kontron) and adjusted the FiO_2 accordingly.

Case report

A twenty-four-year-old male presented with a two-week history of cough, pleuritic chest pain, and a twenty-pound weight loss over the preceding three months. On physical examination, there was tracheal deviation to the right, and breath sounds were diminished over the left hemithorax. A chest x-ray revealed a mediastinal mass extending into the left lower lobe; the right lung was normal. Computerized tomography showed an anterior mediastinal mass with compression of the left main stem bronchus and areas of patchy atelectasis in the left lung. Biopsy revealed an embryonal cell carcinoma.

The patient was started on a regimen consisting of vinblastine, cisplatin, and bleomycin which lasted 12 weeks. The total dose of bleomycin was 228 units/m^2 body surface area. No radiotherapy was given. Six days after the end of his bleomycin treatment, the patient was re-admitted for increasing cough and shortness of breath. A chest x-ray showed no change from the pretreatment films. Because of the increasing severity of symptoms, the decision was made to perform a left thoracotomy to remove the tumour mass and possibly perform a left pneumonectomy.

Preoperative pulmonary function studies revealed mild hypoxaemia and a marked restrictive defect (Table I), attributed to atelectasis in the left lung. Haemoglobin was 104 gm/l ; serum electrolytes, blood urea nitrogen, creatinine and urinalysis were all within normal limits.

Eight days after the last dose of bleomycin the patient was taken to the operating room. He was premedicated with 15 mg diazepam by mouth two

TABLE I

Preoperative blood gases		
PaO_2	(kPa)	10
	(mmHg)	75
PaCO_2	(kPa)	5.1
	(mmHg)	38
pH		7.44
HCO_3^-	(mmol/L)	25
BE^-		0.94
FiO_2		0.21
Preoperative pulmonary functions tests		
	Predicted	Observed
FRC (L)	3.02	1.18
RV (L)	1.31	0.59
TLC (L)	5.50	2.21
FEV_1 (L)	3.18	1.25
FVC (L)	3.8	1.58
DLCO corrected for Hgb	27.50	14.31

hours preoperatively and anaesthesia was induced with sodium thiopental and succinylcholine. He was then intubated with a cuffed, single lumen 8.5 mm orotracheal tube and anaesthesia was maintained with oxygen, nitrogen, morphine, pancuronium and enflurane at an inspired concentration of one to two per cent. Body temperature was maintained using a thermal blanket and the nasopharyngeal temperature never fell below 36.8°C . Central venous pressure was monitored with an internal jugular venous catheter, and maintained between 8–12 mmHg. The right radial artery was cannulated with an 18 gauge $1\frac{1}{2}$ inch catheter (Jelco) for the continuous monitoring of systemic pressure. Inspired oxygen concentration was monitored continuously with a fuel-cell oxygen analyzer (Biomarine). Using an aseptic technique, the intravascular PO_2 sensor, with the electrode mounted at the end of the 35-cm filament, was inserted through the arterial catheter and a special stopcock which allowed simultaneous pressure monitoring (Figure 1). To maintain the patency of the cannula and to prevent the collection of platelet thrombi on the electrode, a continuous flushing device (Accufush MX530-Y, Medex Inc.) with a flow rate of 30 ml/hr was used. In addition, intermittent manual flushing with a 6 ml syringe was performed. The intravascular PO_2 was calibrated with *in vitro* analysis

FIGURE 1 Top, the intravascular PO_2 sensor alone. Bottom, the sensor fitted through the stopcock and the Jelco intravenous catheter. The electrode is located at the distal portion of the sensor.

(Radiometer BMS 3 MK 2) of an arterial blood sample at the beginning of the procedure. In addition to the continuous monitoring of the intravascular PO_2 (PivO_2), intermittent samples were taken for blood gas analysis (Table II). All blood samples were capped, placed on ice and analyzed within an hour. Tumour removal and left pneumonectomy were performed and the procedure lasted six hours. Estimated blood loss was 3000 ml and was replaced with warmed bank blood and crystalloid.

The results of the five sets of blood gas determinations and the corresponding PivO_2 readings are shown in Table II. After the initial calibration (set 1), the PivO_2 reading closely approximated the *in vitro* arterial oxygen tension (PaO_2). Set 2 was taken after the chest wall had been opened. Set 3 was taken when the left pulmonary artery was clamped because of uncontrolled bleeding, after which the FiO_2 was increased to 0.4. The left main stem bronchus was clamped forty minutes later. Set 4 was then taken revealing an increase in PaO_2 and

PivO_2 . FiO_2 was immediately decreased to 0.23, leading to a decrease in PaO_2 and PivO_2 (set 5). The apparent discrepancy between intravascular and arterial PO_2 in sample 4 was caused by the transient disequilibrium as the FiO_2 was decreased, the response time of the intravascular PO_2 electrode being approximately 90 seconds. Throughout the procedure, FiO_2 concentration was adjusted to maintain the PivO_2 between 60 and 70 mmHg, a range considered to be acceptable, to minimize the risk of pulmonary fibrosis.

Neuromuscular blockade was fully reversed at the end of the procedure, and the patient was extubated in the operating room. The radial arterial catheter and PO_2 sensor were removed. The patient was allowed to breathe a mixture of oxygen and nitrogen with a FiO_2 of 0.25 for one hour and then room air. Recovery in the intensive care unit was uneventful, and postoperative blood gas results did not differ from preoperative values. Follow-up chest x-rays at one month, two months and six months showed no evidence of right lung damage.

TABLE II Blood gas results

Sample	FiO_2	P_{iVO_2}		PaO_2		$PaCO_2$		pH	Saturation (%)
		kPa	mmHg	kPa	mmHg	kPa	mmHg		
1	0.25	8.8	66	10.9	82	6.5	49	7.31	95
2	0.24	8.9	67	10.4	78	6.3	47	7.35	95
3	0.21	5.9	44	6.4	48	7.3	55	7.30	80
4	0.40	20.1	151	17.3	130	7.1	53	7.31	98
5	0.23	9.7	73	9.2	69	5.7	43	7.39	93

See text for details of sampling times.

Discussion

Bleomycin may exert its cytotoxic effect by fragmentation of DNA molecules through chelation of ferrous ions.⁶ The mechanism by which it causes pulmonary fibrosis is unknown. In patients treated with bleomycin, moderately enriched levels of inspired oxygen may cause pulmonary toxicity at concentrations ordinarily considered benign. While neither the threshold oxygen concentration capable of causing this complication, nor the safe preoperative bleomycin-free interval is known, these two factors probably have a synergistic influence. Thus, in LaMantia's retrospective analysis of bleomycin and anaesthesia, he found that a mean FiO_2 of 0.38 did not result in postoperative pulmonary complications in eleven patients.⁷ However, the mean interval between bleomycin and surgery was eleven months, considerably greater than what was reported in the series of Goldiner and Nygaard where increased pulmonary morbidity was found.^{1,2}

Our patient was at high risk of developing pulmonary fibrosis for several reasons. As the sensitization effect of bleomycin is inversely related to the duration of the bleomycin free-interval,⁸ a short interval implies an increased risk of pulmonary fibrosis, and in our patient, the course of bleomycin was completed just eight days prior to surgery. Most other reports of pulmonary complications described bleomycin-free intervals of four to twelve months.^{1,2,7} Preoperative pulmonary function was abnormal as demonstrated by the pulmonary function tests. In addition, the surgical procedure (thoracotomy and pneumonectomy) is associated with the potential of causing hypoxaemia, thus necessitating an enriched inspired oxygen concentration, possibly higher than what

may be required in order to allow a margin of safety. Optimal anaesthetic management, therefore, is to maintain minimal inspired oxygen concentration compatible with adequate arterial oxygenation. The intermittent sampling of blood gases is not entirely satisfactory because of the inherent time delay between sampling and reporting of results. Inadvertent exposure to a dangerously low arterial oxygen level may therefore result. We successfully achieved our aim by monitoring the arterial oxygen tension *in vivo* continuously using an intravascular PO_2 sensor. Good correlation with *in vitro* determination of arterial blood gases have been reported with critically ill patients⁹ managed in an intensive care unit as well as during hypotensive anaesthesia.¹⁰ The intravascular PO_2 sensor utilizes a Clark-type electrode incorporated at the end of the 35 cm sensor and its performance is not significantly influenced by the use of nitrous oxide and other anaesthetic gases. Halothane, however, can interact electrochemically with the electrode and render the readings spuriously high.¹¹ Accordingly halothane was not used in the anaesthetic management. The use of the intra-arterial PO_2 sensor for continuous monitoring of PaO_2 necessitates arterial cannulation. However, intra-arterial pressure monitoring is often indicated in the management of ill patients undergoing anaesthesia and surgery. Using an 18 gauge catheter, and a special stopcock, the ability to monitor blood pressure and to perform intermittent blood sampling is retained while the *in vivo* PaO_2 is measured continuously. Deposition of platelet thrombi on the electrode can cause under-reading and care must be taken to prevent it. Insertion of a larger cannula (for example 16 gauge) would circumvent this problem, but would increase

the risk of subsequent arterial thrombosis or haemorrhage. We chose to use a smaller catheter and rely on a high flow continuous flush device and intermittent manual flushing.

In patients catheterized for twenty-four hours or more, the risk of subsequent radial arterial occlusion is higher with an 18-gauge catheter compared to a 20-gauge catheter,¹² but no comparable study has been done in cases with a shorter catheterization period. Moreover, a previously reported series of patients managed in a similar manner during hypotensive anaesthesia had no complications.¹⁰ Thus, the risk of using an 18-gauge catheter was deemed justified considering the potential benefits.

Other possible monitors of oxygenation include monitoring of mixed venous oxygen saturation, transcutaneous oxygen tension and ear oximetry. Although the technology of continuous monitoring of mixed venous oxygen saturation (SvO₂) is available,¹³ we do not feel it satisfies our aim. SvO₂ is determined not only by arterial oxygenation and oxygen consumption, but also by the cardiac output. In the face of a normal PaO₂, an adequate SvO₂ is a satisfactory and reassuring monitor of oxygen delivery. However, if used alone, a normal SvO₂ may be associated with either an undesirably low or an unacceptably high PaO₂; therefore, it is difficult and dangerous to adjust the FiO₂ to maintain a minimum SvO₂. Transcutaneous oxygen tension is dependent on the skin blood flow and local metabolism and has not been found to be reliable for monitoring the adult surgical patient during anaesthesia.¹⁴ Ear oximetry has been proved to be accurate under experimental conditions,¹⁴ and is a plausible alternative, but it is difficult to maintain the ear piece in the correct position during a long procedure and the surgical draping further compounds the problem. Moreover, it suffers the similar drawback as monitoring of mixed venous oxygen saturation; because of the nature of the oxygen-haemoglobin dissociation curve, it is easy to increase the FiO₂ to maintain a satisfactory saturation, but it is difficult to adjust the FiO₂ to maintain a minimum oximetry reading. However, it would seem ideal to monitor both arterial oxygen tension and saturation continuously.

In conclusion, we have described the continuous, *in vivo* monitoring of arterial oxygen tension using an intravascular PO₂ sensor as a useful adjunct in

the successful management of a bleomycin-treated patient undergoing thoracotomy and pneumonectomy. The use of this sensor would also seem to be appropriate in other situations where sudden development of hypoxaemia can occur, for example, during one lung anaesthesia or when managing a patient with rapidly deteriorating pulmonary disease.

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Résumé

Les patients soumis à une thérapie à la bléomycine peuvent développer une fibrose pulmonaire. Le risque est accentué par l'anesthésie générale et des cas mortels avec lésions pulmonaires ressemblant à celles de la toxicité à l'oxygène ont été rapportés. L'étiologie n'est pas encore entièrement clarifiée mais l'administration d'oxygène supplémentaire dans la période péri-opératoire a été incriminée comme facteur étiologique. La meilleure conduite per-opératoire est donc l'administration de la plus petite concentration d'oxygène (F_{iO_2}) compatible avec une oxygénation adéquate. Pour atteindre ce but de façon sécuritaire, un monitoring continu in vivo de la pression partielle artérielle d'oxygène serait préférable à l'analyse intermittente des gaz artériels. Nous rapportons le management fructueux d'un patient ayant subi une thoracotomie après l'administration de la bléomycine en utilisant un dispositif de mesure de PO_2 intravasculaire pour obtenir la lecture continue de la pression partielle d'oxygène. L'utilisation et les limites d'un tel dispositif sont discutées.