CLINICAL RESEARCH

Blood gas analysis: effect of air bubbles in syringe and delay in estimation

C K BISWAS, J M RAMOS, B AGROYANNIS, D N S KERR

Abstract

Two common sources of error in blood pH and blood gas analysis were studied. The effect of delay in estimation was studied in 10 volunteers and 40 patients. Syringes were stored at 0°C, (crushed ice), 4°C (refrigerator) and 22°C (room temperature). The pressure of oxygen (P_{O_2}) fell significantly by 20 minutes at 4°C and 22°C but did not change significantly at 0°C for up to 30 minutes. Blood pH, pressure of carbon dioxide (P_{CO_2}), bicarbonate, total carbon dioxide (T_{CO_2}), and base excess did not change significantly for up to 30 minutes at 4°C and 22°C and up to 60 minutes at 0°C.

The effect of air bubbles in the syringe was studied by leaving a single bubble or froth in contact with the blood for one to five minutes in 40 patients. P_{O_2} rose significantly after two minutes' contact with froth and two minutes' contact with the air bubble, and P_{CO_2} fell significantly after three minutes' contact with the air bubble. Size of the bubble had little effect on rates of change. Blood pH, bicarbonate, T_{CO_2}, and base excess did not change significantly after up to five minutes' contact.

For accurate estimation of P_{O_2} and P_{CO_2} it is necessary to avoid frothing, to expel all air bubbles within two minutes, and to inject the sample into the machine within 10 minutes or store the syringe in crushed ice. The requirements for blood pH and base excess measurement are less exacting.

Introduction

Determination of blood gases is essential in critically ill patients. Critical illness is not confined to "normal laboratory working hours," so that most samples must be handled by the emergency service. Ideally, all areas of the hospital which manage seriously ill patients should be equipped with automatic blood gas analysis equipment regularly maintained by technical staff, and all junior staff should be trained in its use.[1] Since such machines cost over £10 000 to buy and several thousand pounds a year to maintain, however, probably many samples in British hospitals will be dealt with by central laboratories using services operated by medical laboratory scientific officers. Samples are drawn by junior staff and must be transported to the laboratory, where they may await the attention of the medical laboratory scientific officer engaged in other duties.

Instructions to medical staff on handling samples include: "avoid drawing air into the syringe," "expel any air bubbles as quickly as possible," and "transport the syringe in crushed ice if any delay is anticipated." Little quantitative information is usually provided on the importance of these sources of error or the limits beyond which samples become unacceptable. We tested the beliefs of junior medical staff about the importance of these precautions by administering a questionnaire to 10 doctors in three large hospitals in Newcastle who had qualified from 10 different British medical schools. Their estimate of the safe storage time at room temperature varied from five to 60 minutes, two being happy to leave the sample for one hour; six expected little or no improvement in storage time from the use of crushed ice. Nine were well aware of the importance of expelling air bubbles but five had an exaggerated impression of the importance of this source of error.

Much information is already available on the errors resulting from storing blood at different temperatures,[2] adding air to shed blood,[3] and adding anticoagulants.[4] None of the papers giving reassuring results discusses the reproducibility of the measurement or the "type 2 error"—that is, the chance that a significant change in the blood pH or blood gases could have been obscured by laboratory error. We therefore re-examined the question using an accurate pH meter, the Corning 168 blood gas analyser.

Patients and methods

Blood gases were measured in samples of venous blood taken from 70 hospital patients. A Venflon needle was inserted into the median cubital vein in the forearm to facilitate anaerobic collection of the

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serial blood samples. Syringe dead space was filled with heparin solution (Pularin, heparin injection *BP* 1000 IU/ml, Duncan Flockhart and Co Ltd) 1000 units/ml. The quantity of heparin was estimated by weighing 10 syringes empty and then filling the dead space. For a 2 ml syringe 44 ± 19 IU of heparin was needed to fill the dead space, whereas 72 ± 15 IU was needed for a 5 ml syringe. The dilution effect of this heparin was about 2% for the 2 ml syringe and less than 1% for the 5 ml syringe, well below the level at which dilution produces a measurable effect on pressure of carbon dioxide (P_{CO_2}), pressure of oxygen (P_{O_2}), or blood pH[4]

Blood samples with a higher P_{O_2} were drawn from 10 patients in renal failure undergoing haemodialysis. The blood samples were drawn from the arterial line during haemodialysis and were therefore derived from the arteriovenous fistula. A further 10 samples of arterialised venous blood were drawn from the back of the hand of healthy volunteers (staff from the department of medicine) after the hands had been warmed at 43°C to produce maximum vasodilatation.

The heparinised samples were injected into the Corning analyser and blood analysed for pH by a glass pH electrode with a flat membrane, a dialysis reference membrane, a 4M KCl bridge, and an Ag/AgCl reference electrode regulated by temperature; for P_{O_2} by an electrode, comprising a glass-platinum cathode, an Ag/AgCl anode, an electrolyte filling solution, and an oxygen-permeable membrane; and for P_{CO_2} by an electrode consisting of a glass pH electrode separated from the blood sample by a spacer saturated with electrolyte filling solution and a membrane permeable to gaseous CO_2. All measurements were performed at 37°C.

True CO_2 and P_{O_2} were calculated from a calibration graph derived from the data of Kelman and Nunn.[5] Plasma bicarbonate, total CO_2 and base excess were calculated from the results according to the nomogram of Siggaard-Andersen.[6]

Reproducibility of method—Two 5 ml samples were drawn in rapid succession and the syringes immediately placed in crushed ice. Measurement was carried out 15 minutes later when the blood samples were fully cooled, at which time our studies (see below), showed that a few minutes' storage had an insignificant effect on blood pH and blood gases. Analysis was carried out twice from each syringe. The machine error was calculated by comparing the results from a single syringe and the total error by comparing the results from two separate syringes.

Effects of temperature and storage—Venous or arterialised samples were drawn in heparinised 5 ml syringes. These were stored either at room temperature (22°C), in a refrigerator at 4°C, or in crushed ice and ice water at 0°C. In the first experiment, on 20 patients, venous blood gas analysis was carried out after five, 10, 20, and 30 minutes' storage by each method. In a second experiment, on 10 patients, venous blood was analysed at five minutes, one hour, and two hours on samples stored in crushed ice and ice water only. In the third experiment arterialised blood from 10 patients undergoing haemodialysis was drawn from the arterial line of the dialysis circuit and stored at room temperature or at 0°C for up to one hour. For the fourth experiment venous blood was arterialised by warming the hands of volunteers at 43°C for at least 10 minutes; samples were studied at 0°C and at room temperature for up to 30 minutes.

Effect of single air bubble in syringe—To simulate the worst conditions likely to be encountered, we introduced 1 ml of air into a syringe and then drew a further 1 ml of blood. This was done with five different syringes in rapid succession. The air bubbles were kept in contact with blood for one, two, three, four, and five minutes before being expelled. To simulate the conditions more likely to be encountered in clinical practice, we repeated this experiment but introduced only 0·1, 0·2, or 0·5 ml of air and then drew blood up to the 2 ml mark. These air bubbles represented 5%, 10%, and 25% of the total volume of the syringe. Each experiment was carried out on 10 patients. Care was taken not to produce froth by shaking the syringe. Blood gases and pH after one, two, three, four, and five minutes' exposure to air were compared with the results in blood not exposed to air.

Effect of froth in syringe—A bad fit between the nozzle of the syringe and hub of the needle or a crack in either syringe or needle may result in a stream of fine air bubbles entering the blood sample. To simulate this we drew 0·1 ml of air into a 2 ml syringe, shook it vigorously, and measured blood gas and pH after two minutes; the results were contrasted with those obtained in the same blood sample not exposed to air.

Statistics—Student's paired *t* test was used to compare the mean value after five minutes' storage with those after 10, 20, 30, 60, and 120 minutes' storage. The same test was used to compare the results in blood drawn anaerobically with those in blood mixed with air for one, two, three, four, and five minutes.

TABLE I—*Effect of storage at 0°, 4°, and 22°C for five minutes compared with 10, 20, and 30 minutes. Results are means ± SE*

Time (min)	P_{O_2} (kPa)	p Value	P_{CO_2} (kPa)	p Value
		Storage at 0°C		
5	5·32 ± 0·16		5·58 ± 0·06	
10	5·03 ± 0·16	NS	5·59 ± 0·15	NS
20	5·17 ± 0·17	NS	5·59 ± 0·15	NS
30	5·10 ± 0·17	NS	5·80 ± 0·14	NS
		Storage at 4°C		
5	5·36 ± 0·16		5·62 ± 0·13	
10	5·08 ± 0·16	NS	5·76 ± 0·14	NS
20	4·84 ± 0·14	p < 0·02	5·85 ± 0·14	NS
30	4·67 ± 0·20	p < 0·02	5·96 ± 0·14	NS
		Storage at 22°C		
5	4·74 ± 0·15		5·85 ± 0·13	
10	4·50 ± 0·17	NS	5·95 ± 0·15	NS
20	3·81 ± 0·20	< 0·001	6·04 ± 0·16	NS
30	3·04 ± 0·38	< 0·001	6·11 ± 0·16	NS

NS = Not significant.
Conversion: SI to traditional units—P_{O_2} and P_{CO_2}: 1 kPa ≈ 7·5 mm Hg.

Results

REPRODUCIBILITY

Analysis of data from 10 normal people showed that intra-assay error was negligible for all variables tested. The machine error (SD) calculated for a single observation for pH was 0·006 unit, for P_{O_2} was 0·02 kPa (0·15 mm Hg), and for P_{CO_2} was 0·028 kPa (0·21 mm Hg). The total errors for the same variables were 0·006 unit, 0·058 kPa (0·44 mm Hg), and 0·220 kPa (1·65 mm Hg). This total error contained a negligible component of machine error in the case of blood gases; it may be regarded effectively as the syringe error.

TABLE II—*Effects of storage at 0°C for five minutes compared with 60 and 120 minutes. Results are means ± SE*

Time (min)	P_{O_2} (kPa)	p Value	P_{CO_2} (kPa)	p Value	pH	p Value	Bicarbonate	p Value
5	5·41 ± 0·27		6·41 ± 0·27		7·39 ± 0·009		30·32 ± 1·05	
60	5·31 ± 0·28	< 0·025	6·46 ± 0·28	NS	7·39 ± 0·006	NS	30·17 ± 1·04	NS
120	4·63 ± 0·26	< 0·0005	6·78 ± 0·25	< 0·0005	7·38 ± 0·006	< 0·05	33·66 ± 1·37	< 0·01

NS = Not significant.
Conversion: SI to traditional units—P_{O_2} and P_{CO_2}: 1 kPa ≈ 7·5 mm Hg.

EFFECT OF STORAGE

There was no significant change in the mean value of pH, bicarbonate, total CO_2, base excess, or P_{CO_2} when venous blood was stored for up to 30 minutes at any of the three temperatures. Blood pH remained constant at 7·41 ± 0·03 at 0°C and 4°C and at 7·40 ± 0·03 at 22°C. Table I shows the results for P_{CO_2}; there was the expected upward trend at all three temperatures but it did not achieve significance. Measurable changes did occur with longer storage; they became significant, though very slight, after 120 minutes at 0°C for pH, bicarbonate, and P_{CO_2} (table II).

The greatest changes were seen in P_{O_2}. At room temperature P_{O_2} fell steadily and the change was highly significant from 20 minutes onwards (table I). There was a similar but much smaller change when syringes were stored in the refrigerator at 4°C (table I). When the syringe was stored in crushed ice there was no significant change at up to 30 minutes but a significant fall from 60 minutes onwards (table II).

We calculated the maximum error that our experiments were likely to have concealed. From the consistency of the results in our preliminary experiments we concluded that there was a less than 5% chance that storage in crushed ice for 30 minutes introduces an error in Po_2 measurement greater than 1·2 kPa (9 mm Hg) or that storage in crushed ice for 60 minutes introduces errors exceeding 0·5 kPa (3·7 mm Hg) for Pco_2 and 0·02 units for pH.

When blood with a higher Po_2 was used the results were similar. At room temperature there was no significant fall in Po_2 during the first 10 minutes but the rate of fall thereafter was greater than in venous blood (figs 1 and 2). When the syringe was stored in crushed ice there was no significant fall in Po_2 at up to 30 minutes (figs 3 and 4) but there was a significant fall between 30 and 60 minutes (fig 3). There was no significant change in Pco_2 or pH at up to 30 minutes either at 0°C or at room temperature.

TABLE III—*Changes in Po_2 and Pco_2 at one, two, three, four, and five minutes after adding 0·1 ml air compared with 0 minute without air. Results are means ± SD*

Time (min)	Po_2 (kPa)	p Value	Pco_2 (kPa)	p Value
0	5·21 ± 0·37		6·12 ± 0·37	
1	5·22 ± 0·34	NS	6·11 ± 0·37	NS
2	5·52 ± 0·30	< 0·0005	6·06 ± 0·49	NS
3	5·59 ± 0·32	< 0·0005	5·73 ± 0·54	< 0·0025
4	5·70 ± 0·35	< 0·0005	5·64 ± 0·52	< 0·0005
5	5·73 ± 0·36	< 0·0005	5·57 ± 0·51	< 0·0005

NS = Not significant.
Conversion: SI to traditional units—Po_2 and Pco_2: 1 kPa ≈ 7·5 mm Hg.

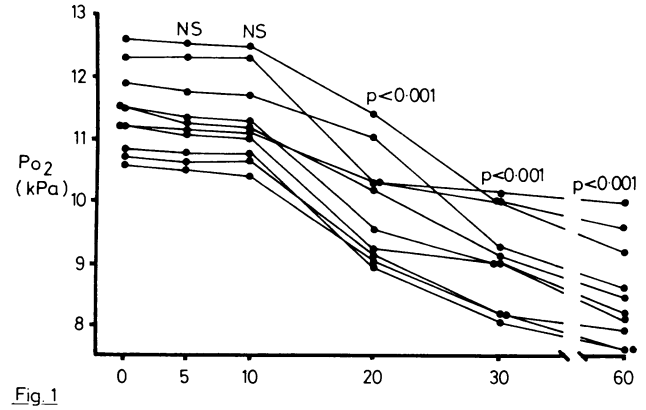

Fig 1

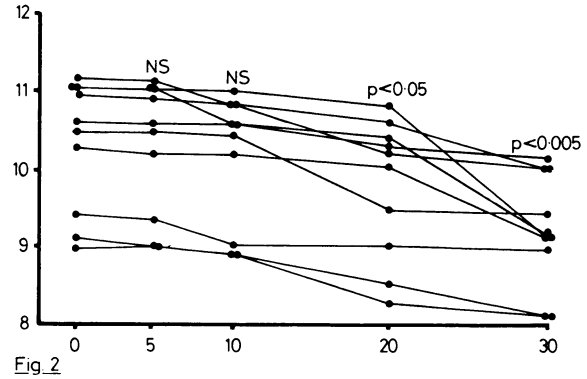

Fig 2

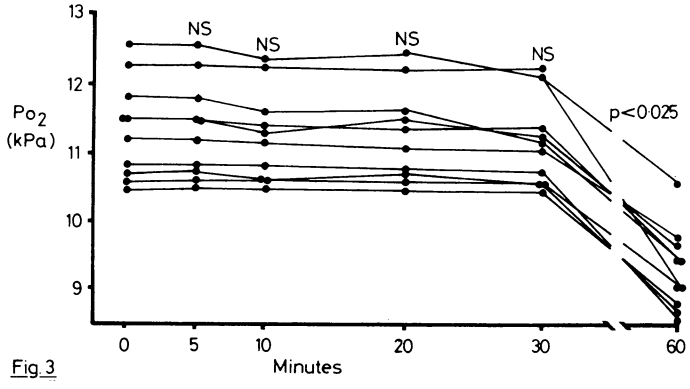

Fig 3

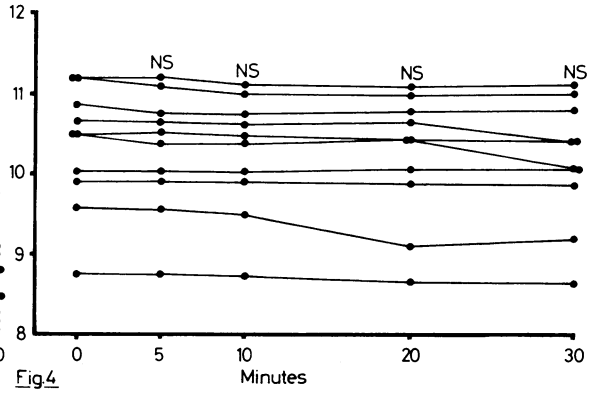

Fig 4

FIG 1—Changes in Po_2 when arterialised blood from arteriovenous fistulas of patients with renal failure was stored at 22°C. FIG 2—Changes in Po_2 when arterialised venous blood from warmed hands of normal subjects was stored at 22°C. FIG 3—Changes in Po_2 when arterialised blood from arteriovenous fistulae of patients with renal failure was stored at 0°C. FIG 4—Changes in Po_2 when arterialised venous blood from warmed hands of normal subjects was stored at 0°C.
Individual results from 10 subjects in each case.
NS = Not significant.
Conversion: SI to traditional units—Po_2: 1 kPa ≈ 7·5 mm Hg.

EFFECT OF AIR BUBBLE

There was no significant change in blood pH after five minutes' exposure to air bubbles varying from 5% to 50% of the volume of the syringe. Significant changes occurred in Po_2 after two minutes and in Pco_2 after three minutes' contact with the air (tables III, IV, and V). Though the changes after one minute were not significant they followed the same trends as those observed later, suggesting that alterations in these two variables occur within one minute. Figure 5 shows the different sizes of bubbles used; there was surprisingly little difference in the rate of change of Po_2 and Pco_2 with bubble size.

EFFECT OF FROTH

There was a substantial change in Pco_2 and Po_2 within two minutes when blood was exposed to froth (fig 6).

Discussion

Placing a syringe in the refrigerator at 4°C is clearly not an adequate substitute for placing it in crushed ice. Storage at any temperature above 0°C results in a fall in Po° due to respiration by blood cells, particularly white cells and reticulocytes.[7] There are corresponding changes in Pco_2 and bicarbonate but these are proportionately smaller because of blood buffering. As would be expected, cooling the blood slows the rate of cell metabolism considerably. Placing the container in a refrigerator surrounded only by air is less effective than immersing it in crushed ice.

If the rate of oxidation by blood cells is independent of Po_2 the oxygen consumption per volume per minute should be the same in venous and arterial blood. This would be expected to cause a steeper fall in Po_2 with arterial blood than with venous blood because of the shape of the oxygen dissociation curve. Since most of our experiments were performed with venous blood, we repeated the storage studies with blood of high Po_2 taken from the arteriovenous fistulas of patients with renal failure and from normal subjects with maximally dilated hand veins. The fall in Po_2 was indeed steeper but the difference was

TABLE IV—*Changes in Po_2 and Pco_2 one, two, three, four, and five minutes after adding 0·2 ml air compared with 0 minute without air. Results are means ±SD*

Time (min)	Po_2 (kPa)	p Value	Pco_2 (kPa)	p Value
0	5·21 ± 0·37		6·12 ± 0·37	
1	5·24 ± 0·33	NS	6·11 ± 0·37	NS
2	5·53 ± 0·41	<0·0005	6·06 ± 0·47	NS
3	5·63 ± 0·38	<0·0005	5·66 ± 0·44	<0·0005
4	5·71 ± 0·36	<0·0005	5·61 ± 0·46	<0·0005
5	5·79 ± 0·34	<0·0005	5·51 ± 0·44	<0·0005

NS = Not significant.
Conversion: SI to traditional units—Po_2 and Pco_2: 1 kPa ≈ 7·5 mm Hg.

TABLE V—*Changes in Po_2 and Pco_2 one, two, three, four, and five minutes after adding 0·5 ml air compared with 0 minute without air. Results are means ±SD*

Time (min)	Po_2 (kPa)	p Value	Pco_2 (kPa)	p Value
0	5·21 ± 0·37		6·12 ± 0·37	
1	5·25 ± 0·31	NS	6·11 ± 0·37	NS
2	5·54 ± 0·24	p<0·0005	6·06 ± 0·41	NS
3	5·65 ± 0·22	<0·0005	5·62 ± 0·44	<0·0005
4	5·76 ± 0·18	<0·0005	5·49 ± 0·45	<0·0005
5	6·03 ± 0·26	<0·0005	5·31 ± 0·47	<0·0005

NS = Not significant.
Conversion: SI to traditional units—Po_2 and Pco_2: 1 kPa ≈ 7·5 mm Hg.

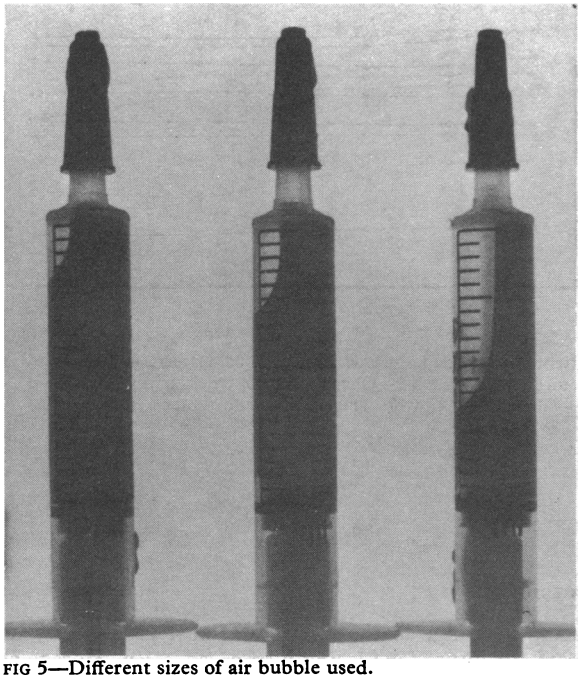

FIG 5—Different sizes of air bubble used.

not as great as might be expected from theoretical calculations, and the precautions that need to be taken when handling blood of normal or reduced Po_2 are similar.

The rise in Po_2 and fall in Pco_2 when an air bubble is introduced into the syringe represent diffusion of oxygen across the fluid-air barrier. Our studies suggest that when a single air bubble is present in the syringe the rate of this process is not critically dependent on the size of the air bubble—a rather surprising finding, which we cannot explain.

A significant change in Po_2 was observed after two minutes and in Pco_2 after three minutes, but there was a trend in the same direction at one minute. We calculate that there is a less than 5% chance that the change caused by one minute's contact with a large air bubble will be greater than 0·45 kPa (3·4 mm Hg) for Po_2 and 0·18 kPa (1·4 mm Hg) for Pco_2. Our studies were carried out under conditions likely to produce a maximum error: contact between venous blood of low Po_2 and high Pco_2 in a large air bubble. The error introduced in practice will often be smaller. It is usually possible to draw an arterial blood sample and expel any trapped air bubbles within two minutes, and provided that this is done the sample will be acceptable for blood gas analysis.

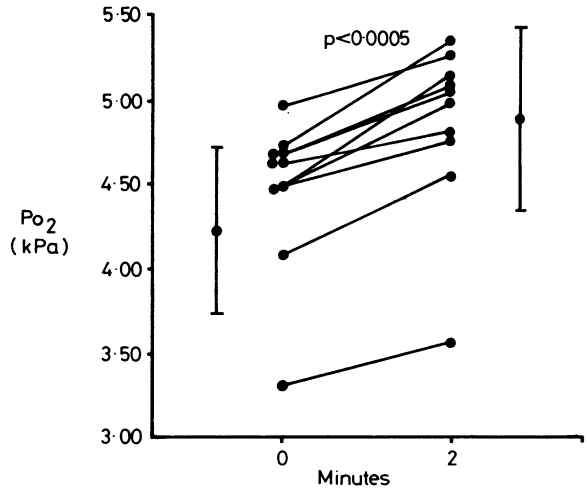

FIG 6—Change in Po_2 of venous blood after adding 0·1 ml air to 2 ml blood in syringe and shaking vigorously. (Mean ±SD and individual results in 10 patients.
Conversion: SI to traditional units—Po_2: 1kPa ≈ 7·5 mm Hg.

The effect of leaving air bubbles in the syringe for longer was studied by Madiedo and colleagues.[8] They showed that the continued presence of an air bubble occupying 10% of the blood volume caused a significant rise of Po_2 within 20 minutes. Our study suggests that some significant change occurs within two minutes. We see no reason to allow air bubbles to remain in the syringe after it is disconnected from the patient, so that this source of error should not arise.

Even a modest amount of froth in the syringe gave rise to a substantial error within two minutes, suggesting that any syringe with visible froth should be regarded as unsuitable for measuring blood Po_2, though it remains suitable for measuring blood pH, Pco_2, and bicarbonate on the rare occasion when these are required in isolation.

RECOMMENDATIONS

A stop-watch or watch with a single hand should be available when blood is drawn for blood gas analysis, so that the clinician can check that any trapped air has been expelled within two minutes and can record the storage time before blood is injected into the pH meter. Samples containing froth should be discarded.

If medical staff have direct access to a machine and can be sure of injecting the blood within 10 minutes it is acceptable to transport the sample at room temperature.

If there is a technician-operated service or there is any other reason to expect delay syringes should be stored in crushed ice between bloodletting and injection into the machine. Under these conditions the sample is adequate for all purposes for up to 30 minutes.

On the rare occasions when the clinician is concerned only with blood pH and bicarbonate and does not require an immediate reply for management of the patient it is acceptable to store blood at room temperature for up to 30 minutes or in crushed ice for up to 60 minutes, and errors are minimal in samples stored in ice for up to 120 minutes.

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Intravenous naloxone in acute respiratory failure

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Abstract

A 58-year-old man presented with acute on chronic respiratory failure. In the acute stage of his illness an infusion of the opiate antagonist naloxone caused an improvement in oxygen saturation as measured by ear oximetry from 74% to 85%, while a saline infusion resulted in a return of oxygen saturation to the original value. When he had recovered from the acute episode the same dose of naloxone had no effect on oxygen saturation.

These findings suggest that in acute respiratory failure there may be overproduction of, or increased sensitivity to, endorphins.

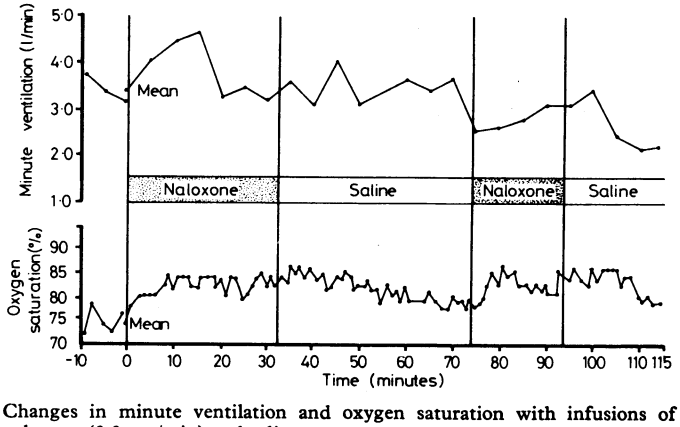
Introduction

Naloxone restores the ventilatory response to added inspiratory loads in some patients with chronic stable airflow obstruction.[1] We report on a patient with acute on chronic respiratory failure in whom naloxone improved both oxygen saturation and tidal ventilation, suggesting that endorphins play a part in acute respiratory failure.

Case history

In 1968 a 46-year-old man presented with recurrent supraventricular tachycardias and was found to have a paralysed right hemidiaphragm, which recovered spontaneously over the subsequent three months. In 1975 he complained of daytime somnolence, which worsened over the next five years, by which time breathlessness limited his exercise tolerance to 50 yards and he was thus admitted to hospital with a respiratory tract infection. He was wheezy and in right heart failure, and had paradoxical movement of the abdominal wall on inspiration. Proximal muscles were weak in his arms and legs. Chest radiography showed that the left hemidiaphragm was paralysed. Results of tests of respiratory function were: forced expiratory volume in one second 0·55 l (predicted 2·6-3·5 l), forced vital capacity 1·60 l (4·0-5·0 l), total lung capacity 6·6 l (5·9-7·2 l), and residual volume 4·5 l (1·9-2·7 l). He required mechanical ventilation for one week, after which he was able to breathe spontaneously. Tests of his respiratory and skeletal muscles after ventilation showed: vital capacity (supine) 1·55 l; vital capacity (erect) 2·15 l; maximal inspiratory pressure 1·9 kPa (19 cm H_2O) (predicted >6·9 kPa (70 cm H_2O)); maximal expiratory pressure 7·8 kPa (80 cm H_2O) (predicted >13·7 kPa (140 cm H_2O)); and transdiaphragmatic pressure 0·3 kPa (3 cm H_2O) (predicted >2·5 kPa (25 cm H_2O)). Electromyography showed evidence of a myopathy of the intercostal muscles. Creatinine phosphokinase concentration was normal. A polygraphic sleep study showed no nocturnal apnoea but periods of hypopnoea associated with falls in oxygen saturation from 75% to 34%. Crossed auditory evoked potentials were normal. A rocking bed improved his episodes of night-time desaturation.

While he was being weaned off the ventilator a bolus of 0·4 mg naloxone intravenously caused an increase in respiratory rate and oxygen saturation (as measured by an ear oximeter). The pH rose from 7·42 to 7·43; oxygen pressure rose from 4·1 to 4·3 kPa (31 to 32 mm Hg); carbon dioxide pressure fell from 8·65 to 8·17 kPa (65 to 61 mm Hg); bicarbonate concentration fell from 36 to 35 mmol(mEq)/l; and base excess fell from +15 to +14 mmol(mEq)/l. A second bolus of 2 mg caused an increase in tidal volume and made him agitated and hot. No opiate drugs had been administered during his admission. Infusions of naloxone (0·2 mg/min) and of physiological saline were compared in a double-blind manner (figure). Five minutes after the beginning of the naloxone infusion minute ventilation rose from a baseline value of 3·12 l/min to 4·64 l/min through an increase in tidal volume, oxygen saturation rising from 74% to 85% over 15 minutes. During saline infusion minute ventilation remained constant and oxygen saturation fell to 75%. When naloxone was restarted oxygen saturation rose to 85% while tidal volume and respiratory rate were unchanged. Minute ventilation fell towards the baseline value on reinfusion of saline.



Changes in minute ventilation and oxygen saturation with infusions of naloxone (0·2 mg/min) and saline.

Regular treatment was started with subcutaneous naloxone (2 mg four times daily). A repeat study three weeks later, when he was well,

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