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Peripheral venous blood gas analysis versus arterial blood gas analysis for the diagnosis of respiratory failure and metabolic disturbance in adults

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ABSTRACT

This is a protocol for a Cochrane Review (Diagnostic test accuracy). The objectives are as follows:

The primary focus of this review is to determine the accuracy of peripheral venous blood gas (PVBG) analysis for diagnosing respiratory failure (RF) or metabolic disturbance (MD) of any type, as demonstrated by abnormalities in tissue pO₂, pCO₂, pH and HCO₃.

BACKGROUND

Arterial blood gas (ABG) analysis allows the direct measurement of important physiological variables such as pH, oxygen and carbon dioxide that are vital for normal organ function. The ABG analysis has long been the standard diagnostic test for respiratory failure and metabolic disturbances, however the more easily performed peripheral venous blood gas analysis is increasingly being performed in a number of clinical settings as an alternative diagnostic test.

Target condition being diagnosed

The target conditions for this review may be summarized under the two headings of respiratory failure and metabolic disturbance.

Respiratory failure (RF) is determined by abnormal partial pressure of oxygen (O₂) and carbon dioxide (CO₂) in the blood. Metabolic disturbance (MD) is diagnosed by an abnormal hydrogen ion concentration in blood as measured by the pH and additional changes in the bicarbonate (HCO₃) concentration.

Respiratory failure (RF)

RF is a major cause of illness and death and occurs as a result of many different disease states in a wide variety of clinical settings. The management of RF depends on the underlying disease or condition(s) as well as the patient's physiological response to these insults. Traditionally it has been the O₂ and CO₂ obtained from the arterial blood gas (ABG) analysis that has led to diagnosis of the type of RF and which has greatly assisted patient management

(Meduri 1996). Type 1 RF occurs as a result of inadequate gas exchange within the lungs and thus results in low blood O₂ concentrations (this may be accompanied by low or normal CO₂). Type 2 RF is caused by a failure to expire sufficient CO₂ from the body through respiration (the O₂ may be low or normal), which leads to a rise in the blood CO₂ levels or hypercapnia.

Diseases such as pneumonia, asthma and pulmonary embolism (PE) are common causes of impaired oxygenation and can rapidly lead to RF and death if the hypoxic deficit is not diagnosed and corrected with O₂ therapy (as well as disease specific treatments). There are other conditions that are more likely to affect the elimination of CO₂ such as chronic obstructive pulmonary disease (COPD), neuromuscular disease, drug overdoses and morbid obesity. These conditions may in fact be worsened by excessive oxygen therapy (Pontoppidan 1972). An accurate assessment of both the O₂ and CO₂ concentrations is therefore vital in the management of patients with RF (Fu 2004).

RF without hypercapnia

Type 1 RF is present when the individual, whilst breathing room air (at sea level and at rest), has a partial pressure of arterial O₂ of less than 60 mmHg in addition to a CO₂ of less than 45 mmHg. The exchange of CO₂ for O₂ down a concentration gradient that occurs between alveolar air and the pulmonary capillary bed of the lungs is termed oxygenation or gas exchange. Oxygenation of blood may be hindered by any process that affects the alveolus (and the delivery of O₂ to it) as well as blood flow to the pulmonary capillary bed (West 1969). The major cause of Type 1 RF is a disturbance in the ventilation/perfusion (V/Q) relationship within each alveolus and its accompanying capillary, or 'lung unit' (West 1969). Those parts of the lung with reduced ventilation due to pathology (pneumonia, asthma, pulmonary haemorrhage) will have reduced O₂ uptake (and to a much lesser extent reduced CO₂ removal) as the affected lung units are perfused with deoxygenated blood but are not being ventilated. This is also called 'pulmonary shunting' and often results in severe hypoxia that is relatively resistant to O₂ therapy (Campbell 1965).

An alternative scenario is that O₂ is able to pass in and out of each alveolus but no gas exchange occurs because there is no perfusion. This will also result in V/Q mismatch. Causes include low cardiac output states, pulmonary embolism and increased intra-alveolar pressure. The final cause of oxygenation failure is any process that affects the alveolar membrane itself, resulting in impaired diffusion of O₂ and CO₂ or a reduction in the total number of alveoli. Examples of conditions that cause abnormalities of diffusion include acute respiratory distress syndrome (ARDS) and fibrotic lung disease.

Isolated hypocapnia without RF

It is important to note that, in addition to reduced O₂, a reduction in the CO₂ concentration (hypocapnia) may indicate an abnormality of ventilation. Hypocapnia suggests respiratory dysfunction and in some cases it may occur prior to overt RF. Depending on the severity of the insult and the number of normally functioning lung units in the individual, this may not cause RF but it may still be clinically important to diagnose. In many cases hypocapnia is caused by an increased rate of breathing (hyperventilation), which may be triggered by the sensation of shortness of breath (dyspnoea) in the individual, and may be due to a wide variety of causes which range from anxiety and panic attacks to life threatening conditions such as pneumothorax and pulmonary embolism. Hypocapnia is defined as a partial pressure of arterial CO₂ of less than 35 mmHg. The relationship between the O₂ and the CO₂ is also important and is incorporated into the Alveolar Gas Equation (Appendix 1), which is discussed later.

RF with hypercapnia

Type 2 RF is present when the partial pressure of arterial CO₂ exceeds 45 mmHg; the O₂ may be either normal or reduced. This will be the primary focus of this review because, unlike Type 1 RF (where there is an alternative non-invasive and reasonably reliable method of diagnosing hypoxaemia using pulse oximetry and oxygen saturation), there is no reliable alternative for CO₂ (with the possible exception of capnography for patients without underlying respiratory disease) (Liu 1992). Because the partial pressure of CO₂ in the blood is determined by the amount of CO₂ being produced by the body and the amount removed by the lungs over time, by ventilation, Type 2 RF is also called ventilatory failure.

Conditions that increase the production of CO₂ include fever, sepsis, infection, obesity and seizures. Individuals with a normal ventilatory system are able to increase their respiratory rate as well as the volume of each breath (minute ventilation) to 'breathe off' the increased amount of CO₂. The rate of CO₂ removal is dependent on the volume of the alveolar dead space (that proportion of each breath that is not involved in the exchange of gases) and the minute ventilation. If, however, the individual has impaired ventilation (reduced ventilatory reserve) or a reduced sensitivity to detecting increased levels of CO₂, or the amount of CO₂ is simply large, elevated blood levels of CO₂ (hypercapnia) and eventually ventilatory failure will result (Manning 1995). Conditions that reduce CO₂ excretion due to reduced minute ventilation that are commonly associated with Type 2 RF include neuromuscular disorders (muscular dystrophy, motor neuron disease), central nervous system disorders (stroke, spinal cord injury, drug overdose), peripheral nervous system disorders (Guillain-Barré syndrome, myasthenia gravis), chest wall disorders (scoliosis, kyphosis, obesity), airway obstruction (asthma, chronic obstructive pulmonary disease (COPD)) and metabolic abnormalities (hypokalaemia, myxoedema).

The presence of acidosis with hypercapnia (termed respiratory acidosis) indicates that the respiratory system is unable to adequately meet the body's gas exchange demands and that the insult is acute (occurring over hours to days). This is because the level of CO_2 in the blood is rising faster than the amount that can be eliminated by the lungs, and also faster than the amount of bicarbonate the kidneys can produce to neutralise the CO_2 (Weinberger 1989). Most commonly there is a combination of these factors that leads to the demand for ventilation exceeding the ability to provide it, resulting in RF and acidosis. When respiratory decompensation occurs quickly (in hours to days), the elevated CO_2 (as carbonic acid) is unable to be adequately compensated for by metabolic processes (by increasing renal bicarbonate retention) and respiratory acidosis results. However, when ventilatory failure occurs over weeks or longer there is often time for the kidneys to increase bicarbonate production in an attempt to maintain a neutral pH within the blood (renal compensation). This can be seen when there is both an elevation in the CO_2 and the bicarbonate (the pH may be normal, low or high depending on the balance) (Dorman 1954).

Patients with hypercapnia may complain of sleepiness, morning headaches, general tiredness, malaise and ankle oedema, while those with RF may present with confusion or delirium. For these reasons, the *British Thoracic Society* recommends a low threshold for measuring arterial blood gas tensions, especially in those patients with any of the aforementioned conditions who may present in RF without significant breathlessness (Myles 2002). The diagnosis of hypercapnia and respiratory acidosis is especially important because the associated morbidity and mortality is high and because effective, evidence-based interventions are readily available. Interventions have been shown to improve patient outcomes, especially for the early initiation of non-invasive ventilation (NIV) to avoid intubation and intensive care admission (and indeed the avoidance of NIV by the administration of the correct fraction of inspired O_2 (FiO_2)), as well as to shorten hospital stays and reduce mortality (New 2006). The efficacy of NIV is well established in patients with respiratory acidosis ($\text{pH} < 7.35$ and $\text{PaCO}_2 > 45$ mmHg) and without contraindications (impaired consciousness, copious respiratory secretions) (Myles 2002). Close clinical monitoring and repeated ABG to monitor the patient's response to treatment is also important.

NIV refers to the administration of mechanical ventilation to a conscious and co-operative patient using delivery devices such as facial and nasal masks that do not require an endotracheal airway (invasive ventilation). In recent years, advances in technology have seen the development of a variety of new machines with easily adjustable settings (such as inspiratory positive airway pressure, expiratory positive airway pressure and the FiO_2). These are able to provide positive pressure ventilatory assistance to the unwell respiratory patient that is less costly and also more comfortable, safe and convenient than invasive ventilation (Mehta 2001).

Metabolic disturbance (MD)

Like RF, MD is a major cause of illness and death due to a wide variety of causes. As with RF the subsequent investigations and management of the patient are dependent on the correct classification of the MD. Traditionally MD can be classified as either an acidosis or alkalosis depending on the pH obtained from an ABG analysis. One can then decide if the primary cause is due to respiratory disease or a renal or metabolic disturbance based on the bicarbonate concentration.

Acidosis

Acidosis is a type of MD that occurs when there is an excessive amount of acid (or insufficient bicarbonate) in the body and a reduction in tissue pH, or acidaemia (typically defined as an arterial pH of less than 7.35). Acidosis may be due to a respiratory or metabolic cause. Regardless of aetiology, the presence of acidosis indicates impaired acid-base homeostasis and is associated with worse clinical outcomes.

Severe acidosis (a tissue pH less than 7.20) results in major organ dysfunction due to adverse effects on intracellular protein function. The pathophysiologic consequences of severe acidosis include reduced muscle strength, reduced muscle contractility, vasoconstriction, arterial dilation, reduced cardiac output, increased metabolic demand and reduced glucose uptake into the tissues. Acidosis also causes potassium to leave cells, which results in hyperkalaemia and a catabolic state that impairs brain function, eventually resulting in obtundation and coma (Adrogue 1998).

Metabolic acidosis occurs with a reduction in tissue pH in the presence of an appropriate ventilator response (increase in ventilation). Typically the ABG analysis demonstrates a reduction in the bicarbonate (HCO_3) as well as the pH and pCO_2 . There are a number of causes of metabolic acidosis but all are potentially life threatening and many require specific treatment based on the aetiology (Eizadi-Mood 2005). Management of metabolic acidosis is assisted by the calculation of the 'anion gap', which is a method for determining the presence of anions (negatively charged ions) that are not measured in standard blood chemistry tests (see Appendix 2). A high anion gap suggests the presence of endogenously produced acids. Clinical examples include diabetic ketoacidosis, lactic acidosis, alcoholic intoxication, drug overdose and renal failure (Brandenburg 1998). In contrast, a normal anion gap metabolic acidosis is seen when there is loss of HCO_3 from the kidneys or gastrointestinal tract, or when there is failure of the kidney to excrete potassium as occurs in renal tubular acidosis (Kraut 2010).

Alkalosis

An alkalosis is another type of MD that occurs when there is an excess of HCO_3 (or insufficient acid) in the body that results in an increase in tissue pH (usually defined as an arterial pH of

greater than 7.45). Similar to an acidosis, alkalosis may be due to a respiratory or metabolic cause. Respiratory causes of alkalosis include hyperventilation, which results in a reduction in CO₂ in the blood as it is breathed off by the lungs. There are a number of reasons for hyperventilation, which range from panic attacks and anxiety disorders to asthma exacerbations and even stroke or head injury (Stocchetti 2005).

A metabolic alkalosis may be caused by a loss of acid as a result of vomiting, dehydration or renal losses (due to renal disease or medications such as diuretics). It is an important condition to diagnose as it is often accompanied by electrolyte imbalances such as hypokalaemia (low potassium), which can result in cardiac arrhythmias and death (Seldin 1972).

The standard means of diagnosing these target conditions (RF with or without hypercapnia, MD with acidosis or alkalosis) has been ABG. The ABG is a diagnostic test that is performed on arterial blood after it is collected from an individual using a needle and syringe; the blood is analysed by a semi-automated machine (blood gas analyser). The arterial puncture is usually performed at the radial artery (of the wrist) as the artery is relatively superficial, easy to palpate and to stabilize, and usually has a good collateral supply from the ulnar artery. Typically, 1 to 2 ml of blood is aspirated using an aseptic technique, any air bubbles are removed to avoid gas equilibration between the air and blood, and the sample is analysed promptly (the arterial gas tensions change over time due to cellular respiration) (Theodore, 2012).

Index test(s)

Peripheral venous blood gas (PVBG) analysis was first described as an alternative to ABG sampling by Dautrebande, Davis and Meakins in 1923 when they measured the CO₂ content of venous blood obtained from the basilic vein in four experiments and found a close correlation with that of arterial blood if the hand was immersed in hot water (Harrison 1965). Since this time the PVBG has been used for the detection of acid-base disturbances in a variety of clinical environments, although some variables have limited accuracy (Gokel 2000; Toftgaard 2008).

The PVBG is increasingly used in a variety of ambulatory and hospital settings including in patients presenting to the emergency department (Lim 2010). In many cases it has been proposed to be suitable as a screening test for acidosis and hypercapnia as well as for titrating O₂ therapy and the diagnosis of acid-base disturbances (Brooks 1959; Gennis 1985). There are, however, a number of physiological differences between peripheral venous and arterial blood (Chu 2003).

Firstly, there is O₂ consumption by the tissues immediately distal to where the peripheral venous blood has been sampled. This changes the affinity of the haemoglobin molecule to CO₂ under the principals of the Haldane effect (deoxygenated haemoglobin is more readily accepting of hydrogen ions generated in the tissues). Alterations to an individual's circulatory system will af-

fect the speed of venous return and thus the O₂ and CO₂ tensions (Mark 1991). When venous return is reduced (such as occurs during cardiac failure, RF, pulmonary hypertension or angiotensin II blockade) there would be an increase in peripheral venous CO₂ relative to arterial blood. Conversely, when venous return increases, such as with chronic hypoxia (due to arterial vasodilation) and high output cardiac states, there is less time for O₂ to be depleted from the returning peripheral venous blood and venous CO₂ may be lower than the expected arterial value. Differences in the method of PVBG collection may also affect the accuracy and reproducibility of the analysis (Ibrahim 2008). The anatomical site of venous blood sampling is important because the characteristics of the PVBG reflect the metabolism of the tissues from which the sample has come. A vein on the dorsal aspect of the hand, for example, has venous drainage from tissues that are less metabolically active than a vein in the cubital fossa which has supplied the larger muscles of the forearm. The use of a tourniquet for venous blood sampling may also alter the characteristics of the pH, pO₂ and pCO₂. Finally, there is the less common 'arterialization' of venous blood that occurs through arterio-venous shunting in the skin or other peripheral tissues that results in peripheral venous values for CO₂ and O₂ concentrations approximating those of arterial blood. This is seen in sickle cell disease during a vaso-occlusive crisis but may also occur with arterio-venous fistulas, steal syndromes and traumatic brain injury (Nahavandi 2002).

The major advantage of PVBG estimation is the ease with which the blood sample can be obtained. The PVBG sample can be simply obtained from a peripheral limb vein at the same time as vascular access is established and other serum blood test investigation samples collected. This eliminates the need for a second blood sample to be collected from a separate site, and reduces the potential for needle stick injury as well as the vascular complications and trauma associated with an arterial puncture (Kelly 2005). Successful sampling from an artery is more difficult than venous cannulation and requires some additional training and skills. Venous blood may be obtained in error, which may lead to diagnostic uncertainty. As with the ABG, the PVBG sample should be analysed promptly after collection to avoid degradation of the contents and inaccuracy (or immediately cooled to 5 °C if there is a delay of more than a few minutes).

Clinical pathway

The current diagnostic pathway for an unwell patient suspected of RF or MD is to perform an ABG, usually after having obtained a clinical history, vital signs (the respiratory rate, heart rate, blood pressure, oxygen saturation and temperature) and physical examination. In some circumstances such as acute resuscitation, intensive care or anaesthesia, the ABG is as important as the vital signs in understanding the patient's pathophysiology. Using the results of the ABG, the clinician is firstly able to determine if the patient has a normal or abnormal pH (acidotic or alkalotic), and then by

looking at the $p\text{CO}_2$ and HCO_3^- he or she can decide if this is due to a respiratory or metabolic cause and whether compensation has occurred (allowing the diagnosis of clinical states such as metabolic acidosis, respiratory acidosis, metabolic alkalosis or respiratory alkalosis). Knowledge of the abnormal values for the $p\text{CO}_2$ and $p\text{O}_2$ also allows the clinician to determine the presence or absence of RF (see [Target condition being diagnosed](#)). Those patients found to have the target condition(s) then go on to have further directed investigations in addition to the initiation of treatment (such as NIV in the case of Type 2 RF).

The ABG (hereafter referred to as the reference standard) is widely available and provides important diagnostic information that is used in the clinical management of patients. It allows the direct measurement of the pH, $p\text{O}_2$ and $p\text{CO}_2$ (as well as electrolytes) from arterial blood and is considered the gold standard. In addition, there are additional calculated (or derived) values that can be obtained from the directly measured variables. These assist the clinician in understanding the underlying cause and thus how the disturbance may be corrected. Examples of calculated ABG values include the bicarbonate (calculated from the $p\text{CO}_2$ and pH), the alveolar to arterial gradient (A-a gradient, calculated by the Alveolar Gas Equation (see [Appendix 1](#)), the anion gap, and Winter's equation for calculating the expected $p\text{CO}_2$ in the presence of metabolic acidosis.

In many institutions around the world the PVBG is replacing the ABG as the initial diagnostic test for RF and MD ([Bilan 2008](#); [Kelly 2001](#); [Ma 2003](#)). When used in this way, patients found to have the target condition(s) are commenced on treatment or else they continue down a more directed line of investigation to ultimately diagnose the cause of their presentation or deterioration ([Treger 2010](#)). Patients without the target condition(s) may be reassured and in some cases no further investigation or treatment will be provided. With this potential to affect patient management, the performance of the PVBG in diagnosing the target conditions (as compared to the reference standard) is paramount.

Rationale

The serious morbidities and mortality associated with RF and MD are well recognized ([Jeffrey 1992](#)). The use of ABG analysis has provided clinicians with an accurate diagnostic test for the detection of RF, acidosis or alkalosis and other variables (such as base excess and bicarbonate), in fact the ABG is the standard by which these conditions are defined. In patients with RF or MD, or both, the results of the reference standard guide management and therefore have an important and established role in clinical practice worldwide. However, ABG sampling is painful and may result in a variety of complications including arterial spasm, intraluminal clotting, bleeding and haematoma formation ([Williams 1998](#)). PVBG has been proposed as an alternative to the reference standard for the detection of hypercapnia (and therefore RF) as well as MDs such as acidosis ([Kelly 2002](#)). Venous blood sampling may be associated with fewer vascular complications than the reference standard. If the PVBG is sufficiently sensitive and specific in the diagnosis of these conditions (compared to the reference standard) then it would provide a more convenient and less painful alternative for clinicians and patients alike.

Venous blood returns de-oxygenated haemoglobin (carrying a greater percentage of CO_2 compared to O_2) to the right side of the heart prior to entering the pulmonary vasculature for gas exchange, it is therefore expected that the PVBG will have significantly less oxygen, more CO_2 and a (slightly) lower pH compared to the ABG which contains newly oxygenated blood ([Rees 2009](#)). Clinicians' common sense would therefore attest that venous samples are good for diagnosing MDs (such as acidosis, alkalosis and compensated states) and that arterial samples are best for diagnosing oxygenation problems. The critical question is whether this is always the case, or is it that the relationships between venous and arterial CO_2 , pH and O_2 change with different disease states or technical factors (such as sample site or time delay between the index and reference standard) as is known to occur with oxygen saturations and changes in blood pH ([Figure 1](#)).

Figure 1. Oxygen dissociation curve (reprinted with kind permission of the BMJ Publishing Group Ltd) (New 2006).

If the PVBG is sufficiently sensitive in diagnosing the diseased (the target condition(s)) when compared to the reference standard then the number of false negatives will be small. In the case of RF with hypercapnia, this would mean that very few (if any) patients with hypercapnia would be missed as a result of having the PVBG performed in place of the ABG. However, a low rate of false negatives may mean that the number of false positives (patients diagnosed with the disease incorrectly) is increased. For RF this would be those patients that are diagnosed with hypercapnia as a result of their PVBG when in fact they do not have an increase in pCO₂ when it is measured by the reference standard. This results not only in a misdiagnosis of RF but in some cases could mean that the patient commences inappropriate investigations or treatment for

the target condition (such as NIV or an inappropriate reduction in oxygen therapy). The possibility that this could result in further morbidity or even mortality certainly exists.

The PVBG offers several potential advantages over the ABG for the diagnosis of RF and acid-base disorders (such as ease of collection), however a variety of physiological differences between the venous and arterial circulations in addition to variations due to sampling technique and different disease states may result in the PVBG being insufficiently sensitive or specific to justify its replacement of the reference standard.

OBJECTIVES

The primary focus of this review is to determine the accuracy of peripheral venous blood gas (PVBG) analysis for diagnosing respiratory failure (RF) or metabolic disturbance (MD) of any type, as demonstrated by abnormalities in tissue pO_2 , pCO_2 , pH and HCO_3^- .

Secondary objectives

To assess the accuracy of PVBG analysis in diagnosing each specific type of RF or MD, particularly Type 2 RF as demonstrated by tissue hypercapnia. We will assess the accuracy of the PVBG analysis when used to diagnose Type 1 RF, Type 2 RF with hypoxia, acidosis, alkalosis, as well as respiratory dysfunction (as indicated by hypocapnia).

METHODS

Criteria for considering studies for this review

Types of studies

We will consider controlled diagnostic test accuracy studies (case-control or consecutive series) of venous blood gas measurement against the reference standard as part of the analysis. The inclusion of case-control studies will be avoided (because of their greater risk of bias) however this will depend on the total number of studies found as a result of the literature search. Studies should provide data on true positives, false positives, false negatives and true negatives. We will include studies that are reported only in abstract form provided that they include adequate data for an assessment of the methodological quality as well as the necessary data for the analysis. We will not include randomized controlled trials of test-treatment design that are more appropriately analysed as intervention rather than diagnostic test accuracy studies in this review.

Participants

We will include adults of either sex, aged 16 years or older, who have had both a PVBG and ABG collected with minimal delay between sequential sampling (less than 15 minutes). We will include participants suspected of having RF or MDs as well as healthy volunteers (including exercise testing). We will include participants from a wide variety of clinical settings, such as emergency departments, ambulatory care units and intensive care units, acutely deteriorating patients in cardio-respiratory arrest and those undergoing anesthesia in this review as we believe that this reflects the heterogeneity of individuals that undertake the diagnostic test in 'real world' clinical practice.

Index tests

The index test is a blood gas analysis using blood obtained from a peripheral vein (PVBG).

Central venous blood gas, mixed venous blood gas and arterialised earlobe capillary blood gas analyses will not be included in this review.

Target conditions

We will look to diagnose the following target conditions.

1. Respiratory failure (RF) of any kind, defined as an arterial $pO_2 < 60$ mmHg or an arterial $pCO_2 > 45$ mmHg.
2. Metabolic disturbance (MD) of any kind, defined as an arterial pH < 7.35 or an arterial pH > 7.45 or an arterial bicarbonate < 20 mmol/L or an arterial bicarbonate > 28 mmol/L.

We will then look to specifically diagnose the type of RF or MD as well as respiratory dysfunction as indicated by isolated hypocapnia.

1a) Type 1 RF (arterial $pO_2 < 60$ mmHg or < 8 kPa and arterial $pCO_2 < 45$ mmHg or < 6 kPa).

1b) Type 2 RF without hypoxia (arterial $pCO_2 > 45$ mmHg or > 6 kPa and arterial $pO_2 > 60$ mmHg or > 8 kPa).

1c) Type 2 RF with hypoxia (arterial $pCO_2 > 45$ mmHg or > 6 kPa and arterial $pO_2 < 60$ mmHg or < 8 kPa).

2a) MD (acidosis) as indicated by an arterial pH < 7.35 with either excess HCO_3^- (> 28 mmol/L) or insufficient bicarbonate (HCO_3^-) (< 20 mmol/L).

2b) MD (alkalosis) as indicated by an arterial pH > 7.45 with either an excess HCO_3^- (> 28 mmol/L) or insufficient HCO_3^- (< 20 mmol/L).

3a) Respiratory dysfunction defined as isolated hypocapnia (arterial $pCO_2 < 35$ mmHg or < 4.67 kPa and arterial $pO_2 > 60$ mmHg or > 8 kPa).

Reference standards

The reference standard is a blood gas analysis using blood obtained from any arterial vessel. We will include samples measured by either a point of care (POC) blood gas analyser or central laboratory within close proximity to the collection point (less than 10 minutes transit time).

Search methods for identification of studies

Electronic searches

We will search for eligible studies using the following electronic databases: the Cochrane Register of Diagnostic Test Accuracy Studies; MEDLINE, OvidSP (1956 to date); EMBASE, OvidSP (1982 to date); LILACS via the BIREME interface (1982 to date); and CINAHL, EBSCOhost (1980 to date). For searching

databases we will use both Medical Subject Headings (MeSH) and free text search terms as outlined in the Cochrane Handbook of Diagnostic Test Accuracy Reviews (DTAR). The MEDLINE and EMBASE search strategy ([Appendix 3](#)) will be adapted for searching all other databases. The expertise of the Cochrane Anaesthesia Review Group (CARG) Trial Search Co-ordinator will also be sought prior to conducting the electronic literature search. We will also search the following regional electronic bibliographic databases, subject-specific databases, and dissertation and theses databases:

- IndMED;
- KoreaMED;
- Panteleimon;
- PASCAL;
- DissOnline;
- OpenSIGLE.

We will not impose language or age restrictions.

We will use the Turning Research into Practice (TRIP), ISI Web of Science (1950 to date) and Google Scholar databases to identify citations, including any meta-analysis studies, that may have been missed by the aforementioned searches.

Searching other resources

We will search the Science Citation Index to identify any additional published, unpublished and ongoing studies, and check the references of all the relevant studies. We will handsearch the following journals:

- *Acta Anaesthesiologica Scandinavica* (from 1995 to date);
- *American Journal of Respiratory and Critical Care Medicine* (from 1995 to date);
- *Annals of Emergency Medicine* (from 1995 to date);
- *British Journal of Anaesthesia* (from 1995 to date);
- *Canadian Journal of Anaesthesia* (from 1995 to date);
- *Chest, Journal of the American College of Chest Physicians* (from 1995 to date);
- *Critical Care Medicine* (from 1995 to date);
- *Emergency Medicine Australasia* (from 1995 to date);
- *European Journal of Emergency Medicine* (from 1995 to date);
- *European Respiratory Journal* (from 1995 to date);
- *Intensive Care Medicine* (from 1995 to date);
- *The Journal of Emergency Medicine* (from 1995 to date);
- *The Journal of Applied Physiology* (from 1995 to date);
- *The Journal of Thoracic and Cardiovascular Surgery* (from 1995 to date);

- *Thorax* (from 1995 to date);
- *The European Respiratory Journal* (from 1995 to date);
- *American Thoracic Society international conference proceedings* (from 2008 to 2013);
- *International Symposium on Intensive Care and Emergency Medicine proceedings* (from 1997 to 2013);
- *American Society of Anaesthesiologists Annual Meeting proceedings* (from 2000 to 2013).

Data collection and analysis

Selection of studies

Two authors (ALB and PT) will independently and in duplicate select appropriate studies. We will resolve disagreements by discussion or by involving MB as arbiter. We will initially screen studies by the title and abstract and retrieve full reports for potentially relevant studies. For these studies, we will use a predefined electronic spreadsheet to assess and document studies for inclusion and exclusion according to the above selection criteria. We will document study selection in a detailed flow chart.

Data extraction and management

We (PT and ALB) will independently and in duplicate perform data extraction using a predefined electronic spreadsheet. We will resolve any disagreements by discussion or by involving MB as arbiter. We will then transfer data to [Revman 5.2](#).

Assessment of methodological quality

We will assess methodological quality independently and in duplicate (ALB and PT) using a predefined electronic spreadsheet ([Figure 2](#)). We will resolve disagreements by discussion or by involving MB as the arbiter. The four key domains from the QUADAS-2 tool will be used to assess the methodological quality of the included studies ([Whiting 2011](#)). Each of the domains (patient selection, index test, reference standard, and flow and timing) will be assessed in terms of the risk of bias ('yes', 'no' or 'unclear') and the first three domains will also be assessed regarding concern for their applicability to our study objective. As the index test and reference test are both objective measurements, the questions relating to interpretation of results will be scored 'no risk of bias'.

Figure 2. Risk of bias and applicability judgments in QUADAS-2.

Table 1. Risk of Bias and Applicability Judgments in QUADAS-2		
	Item plus signaling questions	Criteria for scoring "yes" "no" or "unclear"
1	PATIENT SELECTION Was a consecutive or random sample of patients enrolled? Was a case-control design avoided? Did the study avoid inappropriate exclusions?	We will score this item "yes" when subjects were consecutively or randomly selected; 90% or more of subjects were evaluated in the hospital (emergency department, medical or surgical ward, operating theatre, intensive care unit); 30% or less were diagnosed with co-morbidities including chronic obstructive pulmonary disease, restrictive lung disease, neuromuscular disease, congestive cardiac failure, diabetic ketoacidosis, drug overdose, obesity (BMI greater than 30), 30% or less of subjects had features of sepsis, shock or hemodynamic instability, 10% or less were receiving cardio-pulmonary bypass and 10% or less of subjects had prior testing during the same episode of care for respiratory failure or metabolic disturbance. We will score this item "no" if one or more of these criteria is not met.
2	INDEX TEST Were the index test results interpreted without knowledge of the results of the reference standard? Are there concerns that the index test, its conduct, or its interpretation differs from the review question? If a threshold was used, was it pre-specified?	As the index test is objective, we will score this item "yes" for all cases. We will score this item "yes" in the following cases: if the authors state that the index test was collected without the use of a tourniquet in 70% or more of subjects; if the order of testing is index test before reference standard in all subjects; if the index test sample was analyzed using the same blood gas analyzer as the reference standard in all subjects, if the authors state the anatomical site of venous blood sample was collected from a peripheral vein (arm, hand or leg excluding femoral veins). We will score this item "no" if one or more of these criteria is not met. We will score this item "yes" if the authors define the cut-points that were used in the diagnoses of the target conditions. This item will be scored "no" if this is not the case.
3	REFERENCE STANDARD Is the reference standard likely to correctly classify the target conditions? Was the reference standard results interpreted without knowledge of the results of the index test?	The ABG is the standard by which RF and MD are defined and thus is able to correctly classify the target conditions (and each subtype). The 2 principal target conditions are; 1. Respiratory Failure; defined as an arterial $pO_2 < 60\text{mmHg}$ or an arterial $pCO_2 > 45\text{mmHg}$. 2. Metabolic Disturbance; defined as an arterial $pH < 7.35$ or an arterial $pH > 7.45$ or an arterial bicarbonate $< 20\text{mmol/L}$ or an arterial bicarbonate $> 28\text{mmol/L}$. We will score this item "yes" in all cases as both the reference standard and the index test are objective and thus are not subject to bias from interpretation.
4	FLOW AND TIMING Was there an appropriate interval between the index tests and reference standard? Did all patients receive a reference standard? Did all patients receive the same reference standard? Were all patients included in the analysis?	We will score this item "yes" in the following cases; if the time between the collection of the index test and reference standard was less than 10 minutes for 90% or more of the subjects; if less than 10% of subjects had a change in oxygen therapy or positive pressure ventilation within 10 minutes of the index test; if the blood gas analyzer used for the analysis of all of the index test and the reference standard samples was located at the same point (either at the point of care analysis or a centralized laboratory); if the time between collection of sample and initiation of the analysis did not exceed 20 minutes for each individual index or reference standard test for more than 90% of subjects. We will score this item "no" if one or more of these criteria is not met. We will score this item "yes" if all subjects received both a venous and arterial sample. All subjects must have undergone arterial sampling in the same manner (an arterial puncture of a limb artery using aseptic technique and a 21–25 gauge needle with a standard blood gas syringe containing no more than 2.5ml of blood volume without air). We will score this item "no" if either of these criteria is not met. This will be scored "yes" if all subjects that underwent venous and arterial sampling were included in the analysis.

Statistical analysis and data synthesis

For each study included, one or more index test results (for each patient) will be treated as separate binary classifiers; the cut point for dichotomization will be based on the definitions given previously for hypercapnia, hypoxaemia, acidaemia, alkalaemia, acidosis, alkalosis, hypocapnia and abnormal bicarbonate concentration. For the diagnosis of RF a cut point of greater than 45 mmHg (6 kPa) will be used for CO₂ or less than 60 mmHg (8 kPa) for O₂. The diagnosis of MD will be made by the presence of any of the following: a pH of less than 7.35 (acidaemia), a pH of greater than 7.45 (alkaemia), an abnormal HCO₃ (greater than 28 mmol/L for alkalosis or less than 20 mmol/L for acidosis). Hypocapnia as an indicator of respiratory dysfunction will be diagnosed by a CO₂ less than 35 mmHg (4.67 kPa). In summary the target conditions are hypocapnia and hypercapnia (CO₂); hypoxaemia (O₂); RF (CO₂ and O₂); acidaemia and alkalaemia (pH); acidosis and alkalosis (pH and HCO₃).

Other relevant patient data that will be collected are detailed in the example data extraction forms and include: patient age, sex, weight, co-morbidities including the presence of chronic lung disease, indication for blood gas analysis, and FiO₂ concentration. Test related data to be collected include: site of blood gas collection, presence of tourniquet, testing location (such as emergency department, operating theatre, intensive care unit), time delay prior to testing, location of blood gas analysis machine (POC or central laboratory). Included studies may report one or more blood gas variables:

1. CO₂ (mmHg and kPa);
2. pH;
3. O₂ (mmHg and kPa);
4. HCO₃ (mmol/L).

Each of these variables will be tallied separately. We will construct 2 x 2 tables of the index test and reference standard to show positive and negative index test results for each of the variables being analysed (Riley 2008). We will use the sensitivity and specificity of each variable measured (or calculated in the case of HCO₃) as the underlying parameter in our calculations.

We will perform a 'two step' conditional analysis. The first phase will determine the presence of RF or MD as per the primary objective and the second phase will only proceed if one or both of the conditions are present (it is conditional on the result of the first analysis).

To describe and visualize the data, we will produce forest plots showing pairs of sensitivity and specificity together with 95% confidence intervals from each study in RevMan (Revman 5.2). If as expected a uniform threshold is found across studies for each variable, then pairs of sensitivity and specificity will be meta-analysed to estimate a summary sensitivity and specificity point us-

ing a generalized linear mixed model (binomial family) approach to bivariate meta-analysis of sensitivity and specificity (Reitsma 2005). If thresholds for one or more of the four variables vary across studies, then the underlying Receiver Operating Characteristic (ROC) curve will be estimated as unified within a Hierarchical Summary Receiver Operating Characteristics (HSROC) model (Harbord 2007).

Stata 12 software (Statacorp 2011) will be used for statistical modelling. This approach allows the calculation of summary estimates of sensitivity and specificity while dealing with sources of variation within and between studies and any correlation that might exist between sensitivity and specificity. Results will be presented as sensitivity, specificity, likelihood ratios, and diagnostic odds ratio as parameter estimates of a HSROC model and as bivariate estimates (logit transformed) (Macaskill 2004). The graphical display will be a sensitivity versus false positive (1 - specificity) plot showing individual study results including the individual study estimates, the summary operating point (summary values for sensitivity and specificity), the 95% confidence region on the operating point, the summary curve of the HSROC model, and the 95% prediction region of the true sensitivity and specificity in a future study (Paul 2010).

Investigations of heterogeneity

We will investigate heterogeneity by exploring the following covariates: patient demographics (for example age, weight and sex); patient co-morbidities (for example chronic lung disease, chest wall deformity and central nervous system disorder such as spinal cord injury), and the indication for blood gas sampling (for example shortness of breath, critical illness, resuscitation, trauma or whilst under general anaesthesia) (Deeks 2005). Assuming that an adequate number of studies are available that report study level covariates, then the investigation of heterogeneity will use models fitted in R package mada version 0.5.4 (Doebler 2012; Holling 2012) running in R version 2.15.3 (R 2012). The mada package implements the bivariate logit model (Reitsma 2005) similarly to metandi, but allows covariates jointly modelled on sensitivity and specificity. The one or more covariates will include continuous (age), dichotomous (sex) and nominal (indication for sampling) types.

Quality items relating to spectrum of patients, technical problems in the conduct of the tests leading to verification and blinding biases, and other domains of the QUADAS tool will be considered as potential covariate (Whiting 2011). These will be incorporated in the bivariate model to examine the effect of potential sources of bias across subgroups of studies.

Sensitivity analyses

The robustness of our findings will be tested using a sensitivity analysis to ensure the results of our review are not dependent on decisions made at the protocol stage. We anticipate the following domains to be relevant: study selection, methodological quality assessment, and statistical analysis. There may be other issues that will be identified during the review process.

The effect of study selection will be assessed by repeating the meta-analysis without abstracts or case series. For methodological quality the analysis will be repeated using only those studies scored as 'yes' for the QUADAS-2 tool and for statistical analysis we will repeat the analysis using a fixed-effect method. The results of the sensitivity analysis for each domain will be reported using a sum-

mary table.

Assessment of reporting bias

There will be no assessment of reporting bias as this is not thought to be useful for diagnostic test studies (Begg 2005).

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* Indicates the major publication for the study

APPENDICES

Appendix I. The alveolar gas equation

Equation 1

$$PAO_2 = (P_b - PH_2O) FiO_2 - PACO_2 [FiO_2 + 1 - FiO_2 / R]$$

Where P_b and PH_2O are ambient and saturated water vapour pressures (respectively).

If $FiO_2 = 0.21$, $R = 0.8$ and body temperature = $37^\circ C$, Equation 1 can be simplified to the following:

Equation 2

$$PAO_2 = (P_b - 47) - \frac{P_a CO_2}{0.21} \quad 1.2$$

Having calculated PAO_2 and measured PaO_2 , the **a/A ratio** can then be obtained at 1 ATA.

The predicted PaO_2 at increased ambient pressure while breathing 21% O_2 may then be obtained from Equation 2.

Equation 3

$$PaO_{2(predicted)} = a/A [(760 \text{ ATA} - 47) - Pa CO_2]$$

Appendix 2. The anion gap equation

$$\text{Anion gap} = \text{Na}^+ - [\text{Cl}^- + \text{HCO}_3^-]$$

Appendix 3. MEDLINE OvidSP search strategy

1. Hypercapnia/ or Acidosis/ or Ventilation-Perfusion Ratio/ or Respiratory Insufficiency/ or (hypercapnia or hypox?em* or acidosis or (ventilation?perfusion and mismatch)).ti,ab. or (failure adj3 (respiratory or oxygenation or hypercapnic or ventilatory)).ti,ab.
2. Blood Gas Analysis/ or ((blood gas* or PVBG or ABG) adj3 analysis).mp.
3. 1 and 2

WHAT'S NEW

Date	Event	Description
3 January 2019	Amended	Editorial team changed to Cochrane Emergency and Critical Care

CONTRIBUTIONS OF AUTHORS

Conceiving the review: Anthony Byrne (AB)

Designing the review: AB, Paul Thomas (PT), Mike Bennett (MB), Nathan Pace (NLP)

Co-ordinating the review: MB, NLP

Undertaking manual searches:

Screening search results:

Organizing retrieval of papers:

Screening retrieved papers against inclusion criteria:

Appraising quality of papers:

DECLARATIONS OF INTEREST

Anthony L Byrne: none known

Michael H Bennett: none known

Nathan Leon Pace: none known

Paul Thomas: has advised and given talks on aspects of respiratory medicine for GSK and Novartis

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Internal sources

- The University of New South Wales, Australia.
- Department of Respiratory Medicine, The Prince of Wales Hospital, Sydney NSW, Australia.
- The Cochrane Anaesthesia Review Group, Rigshospitalet, Copenhagen, Denmark.
- University of Utah, Salt Lake City, UT, USA.

External sources

- No sources of support supplied