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CURRENT TOPIC

Personalised Anaesthesia, Arterial Blood Gases and Tissue Hypoxia: Modulating Postoperative Regeneration and Healing

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Abstract

The fundamental limiting factor of major surgery is the body's ability to regenerate and heal tissue after it has been operated on, but this process must take its own course. Recent evidence is available to show that the method of anaesthesia employed during operative procedures and in particular the maintenance of arterial blood gases (ABG), may have a significant influence on regenerative processes by altering, as the case may be, the degree of hypoxia present within tissues. This narrative review addresses the issue of an individualised plan of anaesthesia, aiming to maintain a constant and progressive improvement in partial pressure of oxygen(PaO_2) and carbon dioxide ($PaCO_2$) in arterial blood, as well as their impact on cellular repair processes. The view taken is that the best results cannot be attained by a rigid generalised state of normoxia, but by individualising the treatment by the means of the arterial blood gas results to achieve ends which will have a bearing upon such factors as hypoxia-inducible factor 1-alpha (HIF1α), which refers to a factor evidenced in the regulation of angiogenesis, collagen synthesis and the processes of wound healing. Important clinical experiments and data were considered, taking into account oxygenation strategies, ventilation policies and methods of checking that support individual arterial blood gas aims with the goal of improving the quality of recovery and outcomes beyond the operative phases.

Key words: Precision medicine; Anaesthesia; Postoperative period; Early goal-directed therapy.

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Introduction

Surgical intervention involves a standard tissue injury that initiates a systemic inflammatory response, which is useful in directing repair mechanisms but can also be harmful, leading to complications of inappropriate inflammation, multi-organ failure and defective tissue repair. The result is a degree of post-operative morbidity, from trivial surgical site infections (SSIs) to gross anastomotic dehiscence, which constitutes an enormous burden to the patient in terms of prolonged length of hospital stay (LOS) and persistent functional deficit.[1] The patient's ability to progress from the inflammatory phase of surgical stress to the proliferative and remodelling phases of tissue repair is largely dependent on the local and systemic physiological responses that occur during the surgery itself. The traditional axioms of anaesthesia practice insisted on

rigid, "one size fits all" target values of human physiology (eg maintenance of a mean arterial pressure (MAP) > 65 mm Hg). The recent introduction of the concept of "personalised anaesthesia" (PA), often equated with modern goal-directed therapy (GDT), recognises that the target values of human physiology are best tailored to the individual patient and depend on co-morbid diseases, the surgical context and the individual host's homeostatic reserve.[2] The critical aspect of PA is the alteration of the precept of merely sustaining the physiological parameters, but to optimise them as far as is practicable. Accordingly, the main considerations of haemodynamics (cardiac output, stroke volume) and the increasingly important issue of oxygen delivery to tissues. Whereas GDT considered it important to confirm with cross-sectional images, (the macro) circulation in its entirety, it has become evident that there are wide parameters with regard to these as in (arterial blood gasses) partial pressure of oxygen in arterial blood (PaO_2), partial pressure of arterial carbon dioxide ($PaCO_2$) with regard to the adjustment of the micro (or cross-sectional) environment which represents a variable of considerable although inadequately used importance in the management of cellular injuries and ultimately the mechanisms which are responsible for recovery.[3]

The objective of this review was to clarify the intricate relationship between intraoperative management of arterial blood gas (ABG) values and the associated processes of tissue regeneration. We hypothesise that individual titration of oxygen and carbon dioxide tensions above generalised normoxia/normocapnia provides a potent clinical parameter for modulating the cellular response to injury. The molecular mechanisms relating oxygen tension was detailed, tissue oxygen tension (PtO_2) and pH to cell healing and it was analysed how modern PA strategies modulate advanced monitoring to individualise ABG targets. Also, the clinical evidence linking ABG optimisation to hard outcomes in tissue regeneration was evaluated.

Tissue regeneration

Tissue regeneration is a highly complex biological process that involves a coordinated cascade of events, including inflammation, angiogenesis and matrix deposition. The master regulator of this whole process is the hypoxia-inducible factor (HIF1α).[4] HIF1α is a transcription factor expressed in all tissues, which allows cells to respond to changes in O_2. In normal O_2 tensions (normoxia), HIF1α subunits are rapidly hydroxylated by prolyl hydroxylase domain (PHD) enzymes. This hydroxylation leads to ubiquitination and rapid degradation of HIF1α by the proteosome.[4] When O_2 tensions are below (hypoxia) a critical threshold (PtO_2 usually < 10 mm Hg), the O_2-dependent PHD enzymes become inactive, leading to stabilisation of HIF1α, which dimerises with HIF1β, translocates to the nucleus and stimulates transcription of hundreds of genes which are vital for survival and repair.[5]

These target genes are directly linked to tissue regeneration. In angiogenesis, for example, vascular endothelial growth factor (VEGF) is crucial for forming the new blood supply to damaged tissue. Similarly, for matrix remodelling, lysyl oxidase (LOX) is essential for collagen cross-linking and the tensile strength of healing wounds, as well as for cell survival. Genes involved in glucose transport and anaerobic glycolysis are also crucial, allowing cells to survive in a low O_2 state.[6] The key to PA is the realisation that a relatively mild and transient "therapeutic hypoxia" or a modulation of the PtO_2, ie, downstream from the PaO_2 level, is needed to trigger the beneficial HIF1α-mediated response.[7]

Historically, peri-operative anaesthesia practice tended to favour liberal oxygen administration with higher inhaled fractions of inspired oxygen (FiO_2) to maximise oxygen delivery. The reasoning was straightforward: more oxygen in the blood results in more oxygen at the tissue level. However, clinical research now appears to demonstrate that hyperoxia is a double-edged sword. As far as its benefit, it may produce, at least theoretically, an increased diffusion distance of oxygen in the ischaemic penumbra.[8] Besides its detrimental effect, the excessive oxygen saturation produces large quantities of reactive oxygen species (ROS) and oxidative stress. ROS can damage cell membranes, DNA and proteins, leading to a self-perpetuating cycle of cell injury and inflammatory reaction that can be detrimental and ultimately hinder the healing process.[9] In addition, the high PaO_2 is a potent peripheral vasoconstrictor and the paradoxical effect may result in reduced blood flow and consequently, reduced oxygen delivery to the microcirculations of important tissues.[10]

Arterial blood gases management

The emerging concept of "therapeutic mild hypoxia" suggests that maintaining PaO_2 slightly less than in the normoxic range (eg 60 to 80 mm Hg), or more correctly, avoiding the high end of hyperoxia, may be advantageous. This approach mitigates the deleterious effects of global hypoxemia while allowing localised delivery of a controlled, mild hypoxic insult (PtO_2) to the surgical field, thereby stabilising HIF1α and signalling repair.[7] PA addresses this narrow therapeutic window more effectively by sophisticated monitoring of the individual patient's oxygen requirements. Loveday et al suggest that other conditioning techniques are available to prevent or lessen the perioperative ischaemia-reperfusion injuries, as it is appreciated that hyperoxia. Both the management of ventilation and the resulting $PaCO_2$ levels profoundly affect tissue perfusion and cellular pH, both of which are essential for regeneration. CO_2 is a potent cerebral and pulmonary vasodilator but a vaguer one in the systemic circulation. Permissive hypercapnia (the intentional rise of arterial $PaCO_2$ levels from the normally accepted range of 38-42 mm Hg to between 45-60 mm Hg) is often employed in conjunction with lung-protective ventilation strategies.[11] Systemic vasodilation often leads to enhanced peripheral and renal perfusion, thereby increasing oxygenation to all non-pulmonary tissues. The variations of $PaCO_2$ levels change blood pH and shift the oxyhaemoglobin dissociation curve to the right or the left. Higher $PaCO_2$ (lower pH) levels displace the curve to the right, facilitating the dissociation of oxygen from haemoglobin at the tissue level, a crucial condition for achieving a higher PtO_2 level in injured or ischaemic tissues.[12] The pH of the tissue will directly influence the enzymatic activity of those enzymes needed to remodel the tissue. The matrix metalloproteinases (MMPs) are strongly affected by pH and their functions are to degrade and rebuild the extracellular matrix. A slight change in the range of pH that can be achieved by "manipulating the $PaCO_2$" can alter the balance between destruction of matrix and its deposition, a factor important in the closure and remodelling of wound material.[13]

Individualised ABG management is not possible with standard $ETCO_2$ and SpO_2 determination and will require their replacement by advanced, accurate continuous physiological variables monitoring. The goal is not a fixed PaO_2 but a context-dependent optimisation of oxygen content and delivery (DO_2).

- **High-risk patient groups:** Patients with pre-existing cardiovascular disease, chronic obstructive pulmonary disease (COPD), or severe sepsis may require a slightly higher PaO_2 to compensate for existing ventilation-perfusion (V/Q) mismatch or impaired oxygen utilisation. For these patients, GDT protocols often target optimal DO_2 (often indexed to body surface area DO_2) while aiming for a tight SpO_2 band (eg 95 % to 98 %) to avoid both hypoxemia and hyperoxia.[14]
- **Organ-specific targeting (lungs):** In thoracic surgery or acute respiratory distress syndrome (ARDS), the priority is lung protection. The use of fraction of inspired oxygen (FiO_2) must be titrated carefully to prevent hyperoxic lung injury, even if it means accepting a lower PaO_2 (eg PaO_2 of 70 mm Hg) to minimise the risk of ROS-mediated damage and subsequent pulmonary fibrosis.[15]

The decision to utilise permissive hypercapnia must be personalised based on the tissue most at risk. In neurosurgical or high-risk cardiac patients, where cerebral autoregulation may be compromised, hypercapnia must be strictly controlled (often maintaining $PaCO_2$ between 35 and 45 mm Hg) to avoid cerebral hyperaemia and increased intracranial pressure (ICP).[16] In patients undergoing major abdominal surgery or those at risk for acute kidney injury (AKI), mild permissive hypercapnia may be considered. By inducing systemic vasodilation and improving DO_2 through the Bohr effect, controlled hypercapnia has been shown in some models to mitigate renal reperfusion injury, potentially accelerating renal tissue repair after insult.[17]

The major challenge of personalised ABG management is the dissociation of arterial blood gas tensions and actual tissue oxygenation. Macro-circulatory parameters, such as MAP, cardiac output (CO) and PaO_2, are not predictive of micro-circulatory flow or cellular oxygen utilisation. PA is thus increasingly dependent upon advanced regional monitoring:

- Near-infrared spectroscopy (NIRS) provides continuous non-invasive measurement of regional oxygen saturation SrO_2, or cerebral oxygen saturation ScO_2 in the brain, SpO_2 in the splanchnic bed. ScO_2 is used to manage corti-

cal oxygenation in patients undergoing high-risk cardiac procedures.[18] Changes in the values of SpO_2 in the gut mucosa assess the most vulnerable circulation. Personalisation thus relates to maintaining SrO_2 values above patient-specific baselines, whereby the PaO_2 and haemodynamic targets are actually translating into adequate tissue perfusion.

- Tonometer-derived PH: Gastric tonometry is difficult but provides a surrogate for splanchnic PCO_2 and local PH shifts, allowing real-time assessment of the adequacy of local perfusion and severity of regional ischaemia.[19] The individualised management of ABG during surgery produces concomitant changes in the cellular environment that enhance or inhibit particular regenerative outcomes. The single most important stimulus for the healing of skin and soft tissue wounds is adequate oxygen tension at the site of injury. Wound healing takes place over four overlapping stages (haemostasis, inflammation, proliferation and remodelling), all of which are exquisitely dependent on tissue pO_2.

Fibroblasts, the cells that make the collagen matrix, are extremely sensitive to oxygen. The induction of HIF1α leads to the stimulation of enzymes such as LOX, which catalyse the cross-linking of collagen, thereby providing tensile strength.[20] A state of low but progressive hypoxia, maintained at the tissue level, ensures that this HIF1α signalling is vigorous.

While chronic deep hypoxia results in poor healing, the transient or moderate hyperoxia that has hitherto been utilised to prevent SSI shows equivocal results. A short perioperative period of hyperoxia may lead to a slight but measurable increase in pO_2 at the wound site, which could enhance the oxidative burst of neutrophils —a crucial bactericidal event in preventing infection.[8] Modern PA has, however, shifted away from simply increasing FiO_2 for its own sake and has focused more on maximising DO_2 to achieve this goal and counteract the risks associated with ROS production, which can result from high FiO_2. It is agreed by most clinicians that adequate DO_2 and prevention of global hypovolemia are infinitely more important than hyperoxia in itself.[14]

AKI and acute lung injury (ALI) form the major causes of mortality after major non-cardiac procedures. The capacity of the lung and kidney to regenerate after an ischaemic or inflammatory insult is determined by the personal ABG target. Kidney tissue is highly sensitive to hypoxia. A personalised GDT aimed at improving the tissue oxygen delivery (DO_2) and frequently utilising mild permissive hypercapnia may be of value in reducing the injury. The signals given by HIF1α are of a protective nature in the kidney, leading to the survival of epithelial cells and the production of growth factors such as VEGF and erythropoietin (EPO), which facilitate recovery.[21] If relapsing hypotension is associated with a relatively hyperoxic situation, then toxic ROS are produced and AKI results. The PA ensures that haemodynamic stability is maintained as the primary priority in managing the gases.

The principle of 'protective ventilation' in itself forms a personal ABG strategy. This refers to low tidal volumes and constantly titrated PEEP tactics to actually protect lung mechanics. Permissive hypercapnia is consequently a direct result of these protective approaches. The fact that the ($PaCO_2$) is higher comes with a cost in that there is a relatively smaller degree of stretch of the tissues, but in particular the lung tissue stretch that leads to lesser inflammatory factors, which is a vital requirement in the long process of regeneration of alveolar and endothelial tissue post-operatively.[11] The need, therefore, is to maximise the PaO_2 for a given mechanical stretch and not try to maximise the PaO_2 in the absolute numerical values.

In orthopaedic and spinal deformities, the rate of fusion (osteogenesis) and cartilage repair is exquisitely sensitive to local pO_2 as well as pH. Bone healing is extremely reliant on HIF1α signalling. Hypoxia drives osteoblast differentiation and facilitates chondrogenesis, the process by which cartilage is transformed into bone during fracture healing. Both HIF1α signalling and its downstream targets (such as VEGF) are essential for successful revascularisation and callus formation.[22] Intra-operative ABG management must therefore ensure that the systemic environment is conditionally favourable to allow for this local hypoxic signalling whilst not having a detrimental effect on general tissue perfusion. The pH of the extracellular matrix (ECM) of cartilage and bone is very sensitive. The subtle pH changes induced by individualised $PaCO_2$ management may affect the solubility and deposition of calcium and phosphate; however, there is still a need clinically to demonstrate that manipulation of intraoperative $PaCO_2$ directly increases the rate of fusion.[13]

Clinical implications, troubles and directions for the future

The incorporation of individualised clinical ABG management into routine perioperative practice represents a complex, multi-layered clinical dilemma. Anaesthesia dictates that the parameters for ABG should not be rigid numbers, but rather dynamic ranges modified by the patient's condition and the inherent surgical risk. Table 1 summarises a conceptual framework for setting individualised ABG targets.

Future research must concentrate on the translationalisation of a molecular cognate to the clinical basis. Development of implantable or minimally invasive optical or electrochemical biosensors that are capable of giving real-time PtO_2 and PH readings at the surgical site. This would allow true cellular-level, real-time, GDT.[26] The incorporation of multimodal monitoring data, PaO_2, SO_2, MAP and CO into machine learning models to predict optimum, patient-specific PaO_2 and $PaCO_2$ trajectory for maximum wound-healing potential.[27] TITAN's guidelines were carefully followed while drafting this manuscript.[28]

Table 1: Conceptual personalised arterial blood gases (ABG) targets based on surgical context

Patient / surgical context	**Primary ABG goal**	**Target range** (conceptual)	**Rationale for target**
Major thoracic surgery (lung protection)	Personalised permissive hypercapnia and controlled PaO_2	$PaCO_2$: 45 mm Hg PaO_2: 70 to 95 mm Hg	Minimises barotrauma and ROS injury; accepts higher PCO_2 to protect lung parenchyma (reduced stretch injury).
High-risk vascular surgery (ischaemia-reperfusion)	Tight normocapnia and mild hyperoxia avoidance	$PaCO_2$: 35 to 45 mm Hg PaO_2: 90 to 150 mm Hg	Aims to optimise DO_2 without causing vasoconstriction or excessive ROS generation during reperfusion.
Neurosurgery / intracranial pressure risk	Strict normocapnia	$PaCO_2$: 35 to 40 mm Hg	Prevents cerebral vasodilation that would increase ICP; maintains cerebral perfusion pressure (CPP).
Routine orthopaedic/soft tissue surgery	Optimise DO_2 via GDT, accept normoxia/mild hypoxia	$PaCO_2$: 40 to 50 mm Hg PaO_2: 80 to 100 mm Hg	Supports local HIF1α signalling for healing; avoids hyperoxia-induced vasoconstriction at the wound site.

**Requires validation via large-scale randomised controlled trials (RCTs); ROS: reactive oxygen species; GDT: goal-directed therapy; PaO_2: partial pressure of oxygen in arterial blood; $PaCO_2$: partial pressure carbon dioxide in arterial blood; DO_2: oxygen delivery;*

Despite strong mechanistic bases, there is a paucity of large randomised controlled trials (RCTs) examining the effect of specific intraoperative ABG targets on long-term tissue regenerative endpoints.[23] Major problems include: Part of the problem is the difficulty in measuring true tissue oxygen tension (PtO_2) at the cellular level continuously, safely and accurately. SpO_2 or ScO_2 are indeed surrogate measures, but do not replace localised wound pO_2 or that of deep organ pO_2.[19] The ABG status is inextricably linked to the haemodynamic and temperature regimes, fluid status and the type of anaesthetic agent used (eg volatile agents affect microcirculation). The effect of PaO_2 and $PaCO_2$ in clinical studies is exceptionally difficult to isolate.[24] HIF1α response to any given PO_2 is profoundly influenced not only by an individual patient's genetic profile but also by epigenetic influences.[25]

Conclusion

The perioperative anaesthetic management of ABG is no longer a question of preserving basic homeostatic determinants; it is an opportunity to manipulate the body's innate ability to regenerate tissues. PA must transcend the limits of macro-haemodynamics and involve the careful titration of both PaO_2 and $PaCO_2$ gases to affect the HIF1α signalling pathway. The evidence suggests that hyperoxia should be avoided due to the chances of injury due to ROS, while controlled and personalised targets for oxygen and carbon dioxide can be invoked in order to optimise tissue perfusion, ameliorate advantages through angiogenesis and remodelling and thereby reduce postoperative complications. A well-coordinated research effort must be undertaken to develop

monitoring possibilities and clinical protocols that utilise the full potential of ABG personalisation in enhancing prognosis and quality of postoperative recovery in patients.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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