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Review Article

Evolution of the concept of oxygen transport in the critically ill, with a focus on children after cardiopulmonary bypass

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Abstract The concept of oxygen transport, defined as the relation between oxygen consumption (VO_2) and delivery (DO_2), is of fundamental importance in critically ill patients. The past 200 years have witnessed a stepwise progressive improvement in the understanding of pathophysiological disturbances in the balance of DO_2 and VO_2 in critically ill patients including those after cardiopulmonary bypass surgery. Intermittent spectacular technological achievements have accelerated the rate of progress. Therapeutic advances have been particularly impressive during the recent decades. Examination of the relation between DO_2 and VO_2 provides a useful framework around which the care of the critically ill may be developed. Until now, only a few groups have used this framework to examine children after cardiopulmonary bypass. The key topics that will be covered in this review article are the evolution of the concept from its early development to its present, increasingly sophisticated, role in the management of critically ill patients, with a focus on children after cardiopulmonary bypass surgery.

Keywords: Oxygen transport; critical care; cardiopulmonary\bypass; congenital heart surgery

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THE CONCEPT OF OXYGEN TRANSPORT, DEFINED AS the relation between oxygen consumption (VO_2) and delivery (DO_2), is one of central importance to those working in the field of critical care medicine. A firm grasp of the basic principles and current measurement techniques is of particular significance. This review will address the evolution of the concept from its early development to its present increasingly sophisticated role in the management of critically ill patients with a focus on children after cardiopulmonary bypass surgery. The fascinating aspect of the history is the continually changing, dynamic interplay between the technological advance facilitating understanding of pathophysiological mechanisms and improvement in clinical care.

Early history of oxygen transport

Some 2500 years ago, the ancient Greeks identified air – along with earth, fire and water – as one of the four elemental components of creation. In 1774, a free-thinking English chemist and maverick theologian named Joseph Priestley found that air is not an elementary substance, but a composition, or mixture, of gases. Among them was the colourless and highly reactive gas he called "dephlogisticated air".[1] Priestley wrote: "The feeling of it in my lungs was not sensibly different from that of common air, but I fancied that my breast felt peculiarly light and easy for some time afterwards. Who can tell but that in time, this pure air may become a fashionable article in luxury? Hitherto only two mice and myself have had the privilege of breathing it". He was the first to suggest a connection between blood and air, and that the combustion of oxygen was essential for life in animals.[2] The French chemist Antoine Lavoisier would soon give the name "oxygen" to "dephlogisticated air". The importance of Priestley's revelation cannot be overstated. Oxygen is the most important substrate carried by the circulation. During the past century, measurement of the rate of VO_2 has become an accepted standard to evaluate body metabolism.

In 1870, the German physiologist Adolph Fick indicated: "During any interval of time, the amount

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of a substance entering a given compartment in the inflowing blood must be equal to the quantity of the substance being removed from the blood by the compartment plus the quantity of the substance leaving in the outflowing blood".[3] From this emerged one of the most celebrated principles in biology. Fick argued: "It is astonishing that no one has arrived at the following obvious method by which the amount of blood ejected by the ventricle of the heart with each systole may be determined directly, at least in animals. One measures how much oxygen an animal absorbs from the air in a given time. During the experiment one obtains a sample of arterial and venous blood; in both the oxygen content is measured. The difference in oxygen content tells how much oxygen each cubic centimeter of blood takes up in its passage through the lungs. As one knows the total quantity of oxygen absorbed in a given time one can calculate how many cubic centimeters of blood passed through the lungs in this time".[4]

At about the same time a fellow countryman Eduard Pflüger wrote: "The cardiovascular system fulfills its physiological task by guaranteeing cellular oxygen supply. Everything else is secondary importance: arterial oxygen content, arterial pressures, blood flow velocity, mode of cardiac work, all are incidental and subordinate; they all combine their actions only in service to the cells".[5] The main ingredients of DO_2 in the body were thus identified at an early stage although it was many years before physiologists were able to capitalise on these observations in a practical sense and considerably longer before there was any apparent impact in the management of the critically ill patient.

Fick developed the principle but never actually measured cardiac output himself. Verification of the Fick principle in humans was accomplished in 1930 by Baumann and Grollman at a time when cardiac catheterisation had yet to be established as a clinical tool. They obtained samples of mixed venous blood by inserting a spinal tap needle just to the right of the sternum; the needle entered the right ventricular chamber by puncturing its wall.[6] Less than 10 years later, the German urologist Werner Forssmann cautiously introduced a "well-lubricated ureteral catheter of four Charreieres thickness" into his own antecubital vein. He stopped the initial experiment because his coworkers felt the procedure was too dangerous, but one week later performed the experiment upon himself without assistance. He examined the position of the catheter by X-ray and observed the passage of the catheter using a mirror that was held by a nurse in front of the fluorescent screen. Forssmann invented cardiac catheterisation in an effort to improve resuscitative techniques by injecting medication directly into the heart; he noted, however, that the "described method offers many new possibilities for metabolic and hemodynamic studies". The direct Fick principle of using VO_2 in combination with arterial and mixed venous blood gases is the oldest method of measuring systemic and pulmonary blood flows; nonetheless, it remains the gold standard.

André Cournand and Dickinson Richards at Columbia University and Bellevue Hospital in the United States rescued Forssmann's technique using which they demonstrated right atrial blood samples to represent "mixed venous blood".[7] Shortly after their demonstration of cardiac catheterisation, they applied this technique to the investigation of traumatic shock. They calculated cardiac output using the direct Fick method by measuring the oxygen content of arterial and mixed venous blood concomitantly with VO_2 from expired gas collected in Douglas bags. In this classical study of severely traumatised shock patients, they demonstrated low flow and hypervolaemia. This fine text celebrates the rediscovery of the importance of oxygen transport and the unified concept of human pathophysiology embodied in critical care medicine. Cournand and Richards along with Forssmann were awarded the Nobel Prize in Physiology or Medicine in 1956 for the development of cardiac catheterisation.

The concept of systemic oxygen transport lay fallow during the 25 years that followed the publication of Cournand and Richard's important studies. Part of the problem was methodological. It was not until Swan et al[8] developed the flow-directed balloon-tipped pulmonary artery catheter, also known as the Swan–Ganz catheter, and the thermodilution method[9] in 1970 for cardiac output measurements that these concepts were routinely applied to critically ill patients. In essence, the major contribution by Swan et al was that they moved the cardiac catheterisation laboratory to the bedside of the critically ill patient.

A group of clinical scientists, most notably William Shoemaker, began to make measurements of cardiac output, DO_2 and VO_2 in critically ill shock patients using the thermodilution method. Shoemaker et al soon demonstrated that a low DO_2 level during surgery and the postoperative period was a predictor of death in patients undergoing extensive surgical procedures for life-threatening illnesses, such as non-cardiopulmonary bypass surgery.[10] Over the past 4 decades, they have pursued the quest for ideal endpoints of oxygen transport in shock, such as haemorrhagic, traumatic, septic and cardiogenic events, requiring non-cardiopulmonary bypass surgery.[11–13] They have repeatedly demonstrated that higher-than-normal values, traditionally called supranormal or optimal, of global haemodynamic and oxygen transport parameters are associated with improved outcomes in adult shock patients.[11–13] The mechanism of their treatment is based on the

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phenomenon of pathologic dependency of VO_2 on DO_2, implying that a reduction in DO_2 below the critical point causes a fall in VO_2. The "pathological dependency" has been considered to be the key mechanism for tissue hypoxia when DO_2 levels appeared in the normal range.[14,15] The frequently used optimal values by Shoemaker et al are cardiac index greater than 4.5 L/minute per m^2, DO_2 index greater than 600 ml/minute per m^2, and VO_2 index greater than 170 ml/minute per m^2. Their results are intellectually compelling in various causes of shock: that is, in non-cardiopulmonary bypass patients; however, this may be a high-risk strategy for the injured myocardium in patients after cardiac surgery, and there are no substantive data to support it as an approach.

The short history of oxygen transport in children after cardiopulmonary bypass surgery

On 6th May, 1953, in Philadelphia, John Gibbon performed the first successful open-heart surgery of atrial septal defect closure with cardiopulmonary bypass using a complex screen oxygenator and roller pumps. The mortality from open-heart surgery remained high, mainly because of oxygenator-related problems. This situation was changed in March 1954 when Clarence Walt Lillehei et al used controlled cross-circulation to correct a ventricular septal defect in an 11-year-old boy. The boy's anaesthetised father served as the oxygenator. Over the ensuing 15 months, Lillehei operated upon 45 patients with otherwise irreparable complex interventricular defects. Although cross-circulation was a major advance, it was not adopted for widespread use because it posed a serious risk to the "donor". Nevertheless, this method paved the way for the open-heart surgery era. That very year, Lillehei et al introduced the first clinically successful bubble oxygenator. He also helped pioneer haemodilution and moderate hypothermia techniques for open-heart surgery, and was by then known as the "father of open-heart surgery". Later, John Kirklin enhanced the heart–lung bypass machine to make it feasible for routine use. Cardiopulmonary bypass surgery is one of the most important forms of therapy in the history of cardiac disease. Over the past six decades, generations of cardiac surgeons have been able to correct CHD. In the early days, only older children underwent primary repair. The introduction of deep hypothermia with circulatory arrest in the 1970s provided the ability to perform primary repair or palliation of some complex defects even in newborns and infants.

In the first two decades since the use of hypothermic cardiopulmonary bypass, VO_2 was a subject of interest only during surgery.[16–18] In the postoperative period, the initial concern was, understandably, of heart injury and reduced cardiac output measured using thermodilution or the dye-dilution technique; the latter was soon abandoned.[19,20] Nonetheless, the thermodilution method using the Swan–Ganz catheter has obvious limitations to clinical application in CHD. The presence of intracardiac shunt and tricuspid and pulmonary regurgitation can significantly affect its accuracy. More importantly, certain complex circulations, for example after the Norwood procedure, bidirectional caval pulmonary shunt, and the Fontan operation, preclude the use of the thermodilution technique because of anatomical – for example, parallel systemic and pulmonary circulations – and methodological – for example, inadequate mixing – limitations.

In the 1980s, shortly after Shoemaker's initial studies, the relation between DO_2 and VO_2 was studied in post-cardiopulmonary bypass patients.[21,22] A hypermetabolic response with increased VO_2 was found.[23] In the first few years of this millennium, Drs George Hoffman and James Tweddell from Children's Hospital of Wisconsin and other groups of clinicians studied oxygen transport in neonates after the Norwood procedure.[24–28] Their studies, however, used assumptions for VO_2 of 160 or 180 ml/minute per m^2, presumably derived from predictive equations to calculate haemodynamics during the early postoperative period. The assumed VO_2 gives a single value for a given patient and makes no provision for the dynamic patient milieu that is inevitable at such a time, inducing substantial intra-individual and inter-individual variations in VO_2.[29]

In the late 1990s, a group of clinical scientists, Andrew Redington, Daniel Penny, and the author, at the Royal Brompton Hospital in London, United Kingdom, successfully adapted respiratory mass spectrometry in mechanically ventilated children to directly and continuously measure VO_2. The concept of mass spectrometry, which measures fractional proportions of substances in a mixture, according to their molecular mass–charge ratios, was first introduced at the end of the 19th century. The recruitment of mass spectrometry into respiratory physiology in the 1940s, and its subsequent refinement over the decades, has established a "state-of-the-art" method for measuring VO_2 using highly accurate and rapid multiple gas analysis. The mixed expirate method developed by Davies and Denison in 1979 enabled the use of the mass spectrometer alone to measure metabolic gas exchange and ventilation volume.[30] VO_2 directly measured using respiratory mass spectrometry, in combination with blood gases and pressures from arteries and veins, allows the measurements of each of the elements of systemic haemodynamics and oxygen transport in varied circulations in children with CHD before and after cardiopulmonary bypass, including systemic and

pulmonary blood flows and resistances, VO_2, DO_2, and oxygen extraction ratio. In the past two decades, a stream of studies by Drs Andrew Redington, Glen Van Arsdell, and the author from the Hospital for Sick Children in Toronto, Canada has been published on children after biventricular repair,[31,32] on infants with one-and-a-half ventricular circulation after bidirectional cavopulmonary shunt palliation[33,34], and, most importantly, on neonates with functionally single ventricular circulation after the Norwood procedure.[35–45] The profile of systemic oxygen transport in the early postoperative period has been carefully examined.[31,32,44] VO_2 in our patients after the Norwood procedure varied in the range of 45–152 ml/minute per m^2, with a mean at arrival to the ICU of 101 ml/minute per m^2, which is substantially lower than the assumed VO_2 of 160 or 180 ml/minute per m^2 in previous studies.[24–28] VO_2 is now realised as an important contributor to the impaired balance of systemic oxygen transport in the early postoperative period.[31,32,44,46] The affecting factors in the current clinical management have also been studied in detail, such as temperature,[31,32] vasoactive drugs,[42,46] and inhaled carbon dioxide, etc.[33–35] A better understanding of the VO_2 and DO_2 relation has helped improve the care of critically ill children after cardiopulmonary bypass.

Current techniques and future developments

Although respiratory mass spectrometry is a desirable method for measuring VO_2, it requires a high level of expertise and is cumbersome to carry out in the often crowded setting of the ICU. It remains a research tool in the clinical setting. Over the years, several user-friendly devices have been developed to measure VO_2 in ventilated patients, among which the Deltatrac II metabolic monitor was the most popular.[47,48] But its accuracy was questionable based on the author's own experience, and it is no longer produced. As an alternative, V(max) Encore metabolic cart (CareFusion, Yorba Linda, California, United States of America) is currently validated to measure VO_2 in ventilated children.[49,50] More recently, the CARESCAPE (GE Healthcare, Waukesha, Wisconsin, United States of America) modular monitors have provided a modular unit integrating both mechanical ventilators and patient monitors for VO_2 measurement. This will hopefully allow the measurements of oxygen transport in daily clinical practice. The production of these new devices reflects an important development of the concept of oxygen transport in clinical management. Nonetheless, it should be borne in mind that gas analysers are, in general, frustrating and should be used with great care.[50] There have been other techniques to monitor oxygen transport, such as central venous oximetry. Central venous oxygen saturation reflects well the overall balance of oxygen transport, but does not distinguish VO_2 from DO_2.[45] Last, but not least, it has become clear that predictive equations to estimate VO_2 introduce large and unacceptable errors and should not be used any longer.[29,51]

On the other hand, there has been rapid development in less-invasive techniques to directly measure cardiac output, which allows the calculation of VO_2 using the reverse Fick principle. Currently, there are many types of such devices, such as the analytical pressure recording method,[52] and partial CO_2 rebreathing,[53] to name a couple. These devices, however, can only measure systemic blood flow, and not other haemodynamic and oxygen transport elements in complex circulations of CHD, such as pulmonary blood flow and resistance.

The monitoring devices of the future should enable clinicians to assess accurately, in a non-invasive fashion, the dynamic changes in oxygen transport in physiological and chemical functions of the vital organs and the cell. Near-infrared spectroscopy introduced by Jobsis in 1977,[54] is a non-invasive technology to monitor regional tissue oxygenation. It depends on the different absorption in the infrared spectrum of oxyhaemoglobin and deoxyhaemoglobin, and thus provides the value of oxygen saturation in a mixture of arteries, veins, and capillaries of the underlying tissue. Because of its relative ease of use, near-infrared spectroscopy has been extensively employed in the cardiac operating room and ICU for continuous monitoring of regional cerebral and splanchnic oxygenation.[35,55,56]

Some new techniques have considerable potential for clinical application to monitor oxygenation at tissue and cellular levels in critically ill patients. Orthogonal polarisation spectral imaging using reflected light allows imaging of the microcirculation non-invasively through mucus membranes – for example, lip, gingival tissue, and tongue – and on the surface of solid organs – for example, brain, heart.[57,58] These examples of advanced technology raise the hope that the present gulf between systemic oxygen transport and organ cellular function will, in due course, be bridged.

Summary

The past 200 years have witnessed a stepwise progressive improvement in the understanding of pathophysiological disturbances that can occur in the process of balancing DO_2 and VO_2 in critically ill patients including those after cardiopulmonary bypass surgery. Intermittent spectacular technological achievements have accelerated the rate of progress. Therapeutic advances have been particularly impressive during the recent decades. The examination of the relation between

DO_2 and VO_2 provides a useful framework around which the care of the critically ill may be developed. Until now, only a few groups have used this framework to examine children after cardiopulmonary bypass. Nonetheless, the loop remains to be closed in terms of demonstrable optimisation of tissue oxygenation. Greater insights into optimising the care for this group of patients in the future will come from further studies of these relations.

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Conflicts of Interest

None.

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