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A new method to measure oxygenator oxygen transfer performance during cardiopulmonary bypass: clinical testing using the Medtronic Fusion oxygenator

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Abstract

Background: There is no acceptable method of testing oxygen transfer performance in membrane oxygenators quickly and easily during cardiopulmonary bypass. Pre-clinical testing of oxygenators is performed under controlled situations in the laboratory, correlating oxygen transfer to blood flow using 100% oxygen. This laboratory method cannot be used clinically as oxygen transfer values vary significantly at each blood flow and the FiO_2 is not kept at 1. Therefore, a formula was developed which corrects the existing FiO_2 to attain a PaO_2 of 150 mmHg: the corrected FiO_2 at 150 mmHg. In graph form, this corrected FiO_2 (x-axis) is correlated to the patient's oxygen consumption levels (y-axis), which determines the membrane oxygenator oxygen transfer performance.

Methods: Blood gas and hemodynamic parameters taken during cardiopulmonary bypass using the Medtronic Fusion were used to calculate the oxygen consumption (inlet conditions to the oxygenator) and the corrected FiO_2 for a PaO_2 of 150 mmHg. Validation of the formula "FiO_2-PaO_2/(Pb-pH_2O)+0.21" was carried out by plotting the calculated values on a graph using PaO_2 values between 145 to 155 mmHg and then, using the corrected FiO_2 for PaO_2s outside of this range.

Results: All trend-lines correlated significantly to confirm that the Medtronic Fusion had an extrapolated oxygen transfer of 419 milliliters O_2/min at an FiO_2 of 1 to achieve a PaO_2 of 150 mmHg.

Conclusions: Use of the corrected FiO_2 correlated to the oxygen transfer conditions of the membrane oxygenator can easily be used on a routine basis, providing valuable information clinically. When used by the manufacturer under laboratory conditions, further clinically relevant data is provided in terms of FiO_2 and resultant PaO_2s instead of the present limitations using blood flow. In this way, a clinically justifiable method has been developed to finally establish a standard in testing membrane oxygenator performance.

Keywords

cardiopulmonary bypass; oxygen transfer; oxygen consumption; membrane oxygenator; FiO_2; PaO_2

Background

As far back as 1972, Galletti wrote, "There is no universally accepted way of measuring gas transfer capacity of artificial lungs."[1] Describing oxygenator gas exchange from clinical data remains difficult because there is no well-accepted technique and it is difficult to compare clinical and laboratory data.[2] These statements hold true today in that the pre-clinical phase of testing membrane oxygenators may provide some information for clinical use, but it cannot be adapted as a method to be used during cardiopulmonary bypass (CPB).

Before release to market, manufacturers use the guidelines set by the Association for Advancement of

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Medical Instrumentation and the International Organization for Standardization (AAMI/ISO:7199 (2009)).[3]

Although these test conditions mimic clinical conditions, they are quite broad, leading to a variability in oxygenator performance and are limited to comparing blood flow to oxygen transfer using 100% oxygen.[4] As a result, it has become common practice to refer to membrane oxygenators in terms of maximum blood flow without reference to the maximum oxygen transfer (O_2T) capabilities of each oxygenator, even though this information is provided in the user's manual supplied with each system. (Figure 1)

During CPB, this method of using blood flow as a parameter to judge membrane oxygenator O_2T performance is of no value as O_2T values vary significantly at each blood flow and the FiO_2 is not kept at 1.

Oxygen transfer across membrane oxygenators depends on the incoming conditions of hemoglobin (Hgb), blood flow and venous saturation (SvO_2), which equals the patient's oxygen consumption (VO_2).

The conditions in which the membrane oxygenator is put under the greatest stress are high Hgb, high blood flow and low SvO_2. This would be equivalent to higher levels of VO_2 or O_2T. The amount of oxygen to be transferred by the oxygenator to re-oxygenate the blood is referred to as the O_2T and is also measured in milliliters O_2/min. It is synonymous with VO_2 as both are calculated using the Fick formula (CaO_2-CvO_2)* blood flow (Appendix 1).

During CPB, the FiO_2 is set to a certain acceptable value to attain a PaO_2 that changes depending on the inlet conditions of the membrane oxygenator (the VO_2) and how effective the membrane oxygenator is in re-oxygenating the blood. The resultant PaO_2, along with the FiO_2, is used to judge how well the membrane oxygenator has performed. The perfusionist responds to PaO_2 results without determining the factors which ultimately effect the end results.[5] To this, the question must be posed: "What was the VO_2 when the blood gas was taken?" In essence: "What were the inlet conditions to the membrane oxygenator?" The next question is: "How do we correlate the various FiO_2 and PaO_2 values to the VO_2?" The FiO_2 and the PaO_2 are treated as separate entities. For this reason, the relationship between the PaO_2 and FiO_2 was evaluated.

The established gas laws, (Dalton's Law of Partial Pressures) states that the sum of partial pressures of individual gases equals a total pressure. The partial pressure of oxygen in room air is 159 mmHg, resulting in an FiO_2 of 0.21, which is calculated from the total barometric pressure (Pb) (159 mmHg/760 mmHg=0.21). Since water vapour pressure (P_{H_2O}) of 47 mmHg dilutes the air, the PaO_2 then becomes:

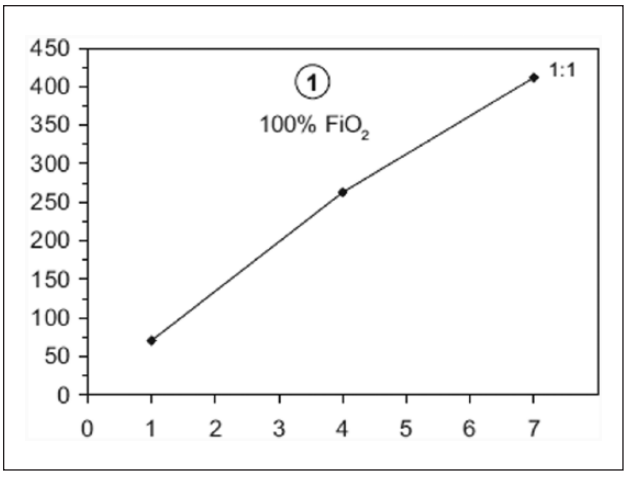

Figure 1. Shows the typical graph printed in the user's manual of the Medtronic Fusion, showing the increase in blood flow (x-axis) up to a maximum O_2T (y-axis). (Permission Medtronic).

(760-47)*0.21=150 mmHg. The end formula for converting the PaO_2 into a fraction becomes: FaO_2=PaO_2/(Pb-47) and, in this way, any PaO_2 may be converted into a fraction (FaO_2). Converting the PaO_2 into a fraction (FaO_2) then allows equal comparison to the actual FiO_2.

It is known and it can be measured that, for every FiO_2 value, there is a maximum PaO_2 (depending on altitude). When a difference exists between the PaO_2 and the maximum PaO_2 that can be attained, the conversion of the PaO_2 into a fraction establishes a reference point to the actual FiO_2.

A difference between FiO_2 and the FaO_2 means that the FiO_2 has not reached its full potential and has reached only a certain degree of oxygenation. In this way, the FiO_2 is divided into two segments; the oxygenated part, known as the FaO_2 and the deoxygenated part, known as the "Anoxic Fractional Difference". The anoxic fractional difference (AFD) is the FiO_2 at which the PaO_2 is essentially zero. AFD= FiO_2-FaO_2. The smaller the AFD, the closer is the actual PaO_2 to the maximum PaO_2.

Adding 0.21, which is a PaO_2 of 150 mmHg, to the AFD will give the corrected FiO_2 ($cFiO_2$). (Appendix 2)

Correlation of VO_2 and $cFiO_2$

There are two essential parts used to determine the O_2T performance of an oxygenator; the calculation of the VO_2 (y-axis) and the calculation of $cFiO_2$:150 mmHg (x-axis).

Figure 2 shows the proposed O_2T reference trendline achieved from the clinical results attained during CPB that is used on a case-to-case basis.

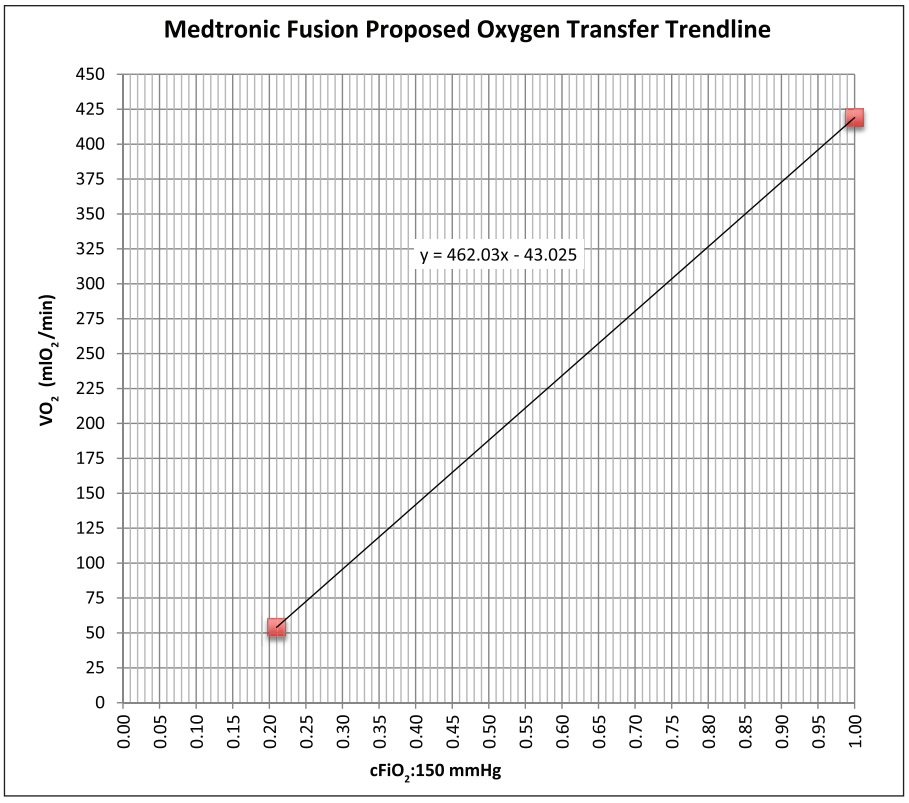

Figure 2. The Medtronic Fusion proposed O_2T trend-line which is used as a guideline in documenting oxygenator performance for clinical cases.

Methods

Study Design

The primary hypothesis of this study was to validate the use of the $cFiO_2$ clinically and to verify the O_2T tests performed by the manufacturers under standard laboratory conditions.

The assessment was conducted between Nov 2012 and July 2015.

All the documented data and blood samples taken during CPB were those that were normally taken during cardiopulmonary bypass. There were no changes made to the perfusion circuit or protocol. All patients gave informed written consent in which the use of any data may be used for study purposes.

Study Participants

All adult patients undergoing CPB using the Medtronic Fusion.

Statistical Analysis

The patient demographics are presented as mean, maximum and minimum. A linear trend-line with two parameters for intercept and slope was used for fitting the data. R^2 coefficients of determination for metric-scale data as well as F-Tests were computed to check the adequacy of the model. The α-level for tests was 0.05.

Cardiopulmonary Bypass

The Medtronic Fusion (Medtronic, Minneapolis, MN, USA®), used in this study, is a membrane oxygenator with state-of the-art integrated arterial filter that was released for clinical use in September 2012. It has polypropylene, plasma-resistant hollow fibers with a surface area of 2.5 m^2 and a priming volume of 260 ml.

The recommended maximum blood flowrate is 7 L/min with an O_2T rate of 415 ml O_2/min (Figure 1).

Our set-up consists of a Stöckert S3 HLM, Medtronic Fusion oxygenator, open-system reservoir, blood cardioplegia with infusion pump (potassium, magnesium), alpha-stat blood gas management, and hypothermia to 34°C. Electronic charting is via the data management (DMS) system (Stöckert, Munich, Germany).

Data Collection

During CPB, arterial and venous blood samples were taken at steady-state (no changes to CPB parameters for a minimum of two minutes). Oxygen consumption and

$cFiO_2$ were calculated using MS-Excel with the following parameters; Hgb, SaO_2, PaO_2, $PaCO_2$, SvO_2, PvO_2, blood flow and FiO_2.

Data Validation

To confirm the maximum PaO_2 at each FiO_2 setting, seven samples from the crystalloid prime at 37 degrees were taken at an FiO_2 of 21, 30, 40, 50, 60, 70, 80 and the PaO_2 measurement was documented. This was repeated on 2 different occasions.

To validate O_2T and predict oxygenator performance, two different methods were employed, with all graphs having the same format; VO_2 on the y-axis and FiO_2 and/or $cFiO_2$:150 mmHg on the x-axis.

Method number one: using PaO_2s in the range of 145 to 155 mmHg and plotting the actual FiO_2 on the x-axis correlated to the VO_2.

Method number two: utilizing all blood gas samples in which the FiO_2 was corrected to a PaO_2 of 150 mmHg, correlated to the actual VO_2.

Lastly, a single case report is presented.

Results

Table 1 gives the pO_2s taken from 37°C crystalloid prime solution of the CPB system, using a range of FiO_2s. The maximum PaO_2 measured by the blood gas machine (Siemens Rapidpoint 405, Siemens, Munich, Germany) is 600 mmHg. Therefore, it was not possible to measure the pO_2s above an FiO_2 of 0.8.

Patient demographics are presented in Table 2, comprising a total of 109 patients (20% females, 80% males) with a total of 414 sets of blood gas samples (arterial and venous simultaneously).

Table 3 and Table 4 show the CPB parameters at 34 and 37 degrees Celsius, respectively.

Twelve percent (54/414) of the blood gases were within the range of 145 to 155 mmHg which could be used at the actual FiO_2 to validate the membrane oxygenator oxygen transfer performance that is presented in Figure 3. Regression analysis using the PaO_2 range of 145-155 mmHg showed an R^2 value of 0.838 ($F(1.51) = 262.8$, $p<0.0001$)

The extrapolated O_2T was 423 ml O_2/min at an FiO_2 of 1 and 44 ml O_2/min at 0.21 FiO_2.

From the whole patient database, Figure 4 demonstrates the VO_2 (y-axis) correlated to the $cFiO_2$:150 mmHg (x-axis). Regression analysis of the corrected FiO_2 of all patient data was 0.804 ($F(1.412) = 1690.0$, $p<0.0001$). The extrapolated O_2T was 415 ml O_2/min at an FiO_2 of 1 and 65 ml O_2/min at 0.21 FiO_2.

Finally, taking the average of Figure 3 and Figure 4, the proposed O_2T reference trend-line in Figure 2 was created, providing an extrapolated O_2T of 419 ml O_2/min at an FiO_2 of 1 and 54 ml O_2/min at 0.21 FiO_2.

Table 1. Shows the resultant PO_2s of the 37°C crystalloid priming for a range of FiO_2s.

FiO_2	PO_2 test 1	PO_2 test 2
0.21	164	156
0.30	255	252
0.40	316	328
0.50	393	404
0.60	451	461
0.70	502	510
0.80	591	599

Table 2. Patient demographics, n=109 patients. Pre-CPB.

Pre-CPB	Average	Min	Max
Age (years)	67.7 ± 10.8	35	87
Height (cm)	173 ± 9.4	146	197
Weight (kg)	87 ± 21.4	49	170
BSA (m^2)	2 ± 0.3	1.5	2.7
Calculated blood flow (2.4 CI)	4.8 ± 0.6	3.6	6.6

BSA: body surface area; CI: cardiac index.

Table 3.

CPB at 34°C	Average	Min	Max
Hgb (gm/dL)	10.0 ± 1.6	5.8	13.2
Blood flow (L/min)	4.6 ± 0.6	3.3	5.8
Cardiac Index (L/min/m^2)	2.3 ± 0.2	1.8	2.8
SvO_2 (%)	75.1 ± 3.8	62.3	87.1
VO_2 index (ml O_2/min/m^2)	81 ± 12	52	109
VO_2 (ml O_2/min)	164 ± 40	78	259
PaO_2 (mmHg)	212 ± 54	126	373
FiO_2	0.52 ± 0.9	0.3	0.7
$cFiO_2$:150 (mmHg)	0.43 ± 0.8	0.24	0.59

Hgb:hemoglobin.

Table 4.

CPB at 37°C	Average	Min	Max
Hgb (gm/dL)	10.4 ±1.5	6.5	13.1
Blood flow (L/min)	5 ± 0.6	3.4	6.3
Cardiac Index (L/min/m^2)	2.5 ± 0.3	1.5	3.7
SvO_2(%)	70 ± 4	58	80
VO_2index (ml O_2/min/m^2)	103 ± 14	65	145
VO_2 (ml O_2/min)	209 ± 45	100	322
PaO_2 (mmHg)	164 ± 39	90	337
FiO_2	0.56 ± 0.8	0.37	0.75
$cFiO_2$:150 (mmHg)	0.53 ± 0.8.6	0.31	0.75

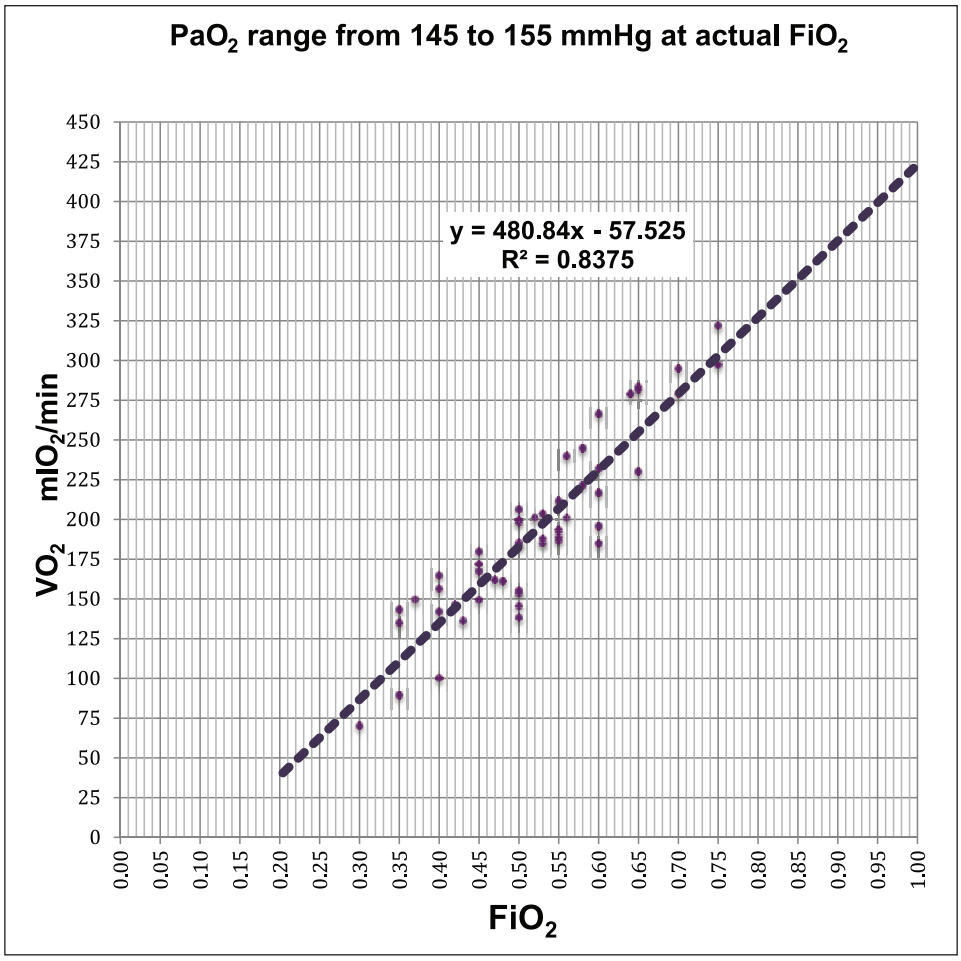

Figure 3. VO_2 (ml O_2/min) versus actual FiO_2 from clinical blood samples of PaO_2s ranging from 145 to 155 mmHg.

Patient example

Our largest patient to date was a 48-year-old male patient with a height of 179 cm, weight of 170 kg, body surface area of 2.74 m^2 and a body mass index of 53% who presented to the operating room with an aortic aneurysm requiring a Bental procedure. Using a cardiac index of 2.4, the blood flow was calculated to be 6.6 L/min. In preparation for CPB, the estimated VO_2 was calculated using 80 ml O_2/min/m^2 at 34°C, 100 ml O_2/min/m^2 at 37°C and 130 ml O_2/min/m^2 for extreme conditions: VO_2 219 ml O_2/min, 274 ml O_2/min and 356 ml O_2/min, respectively. Using Figure 2, the proposed FiO_2 to attain a PaO_2 of 150 mmHg at these VO_2 values would be 0.57, 0.69 and 0.86, respectively. (Figure 5)

During CPB, the PaO_2s attained were 226, 209, 197 and 105 mmHg. The FiO_2 was set at 0.65 at the beginning of CPB and no change was required.

The $cFiO_2$ was calculated as follows and documented on Figure 5.

$$Calculation\ of\ cFiO_2 : FiO_2 - (PaO_2 / 713) + 0.21$$
$$= cFiO_2 : 150\ mmHg$$

$$\text{Blood gas 1}: 0.65 - (226/713) + 0.21 = 0.54$$
$$\text{Blood gas 2}: 0.65 - (209/713) + 0.21 = 0.57$$
$$\text{Blood gas 3}: 0.65 - (197/713) + 0.21 = 0.58$$
$$\text{Blood gas 4}: 0.65 - (105/713) + 0.21 = 0.71$$

The respective VO_2 values at 34°C were 229, 219 and 233 ml O_2/min; at 37°C it was 295 ml O_2/min.

Discussion

Our evaluation using the $cFiO_2$ formula correlated to the VO_2 shows that the Medtronic Fusion has, indeed, surpassed the Association for the Advancement of Medical Instrumentation (AAMI) minimum standard testing, with the capability of transferring at least 419 ml O_2/min at an FiO_2 of 1 attaining a PaO_2 of 150 mmHg and confirms the testing results provided by the manufacturer. The $cFiO_2$:150 mmHg more accurately describes the membrane oxygenator performance, even with changes to the Hgb concentration, blood flow and SvO_2 seen during CPB.

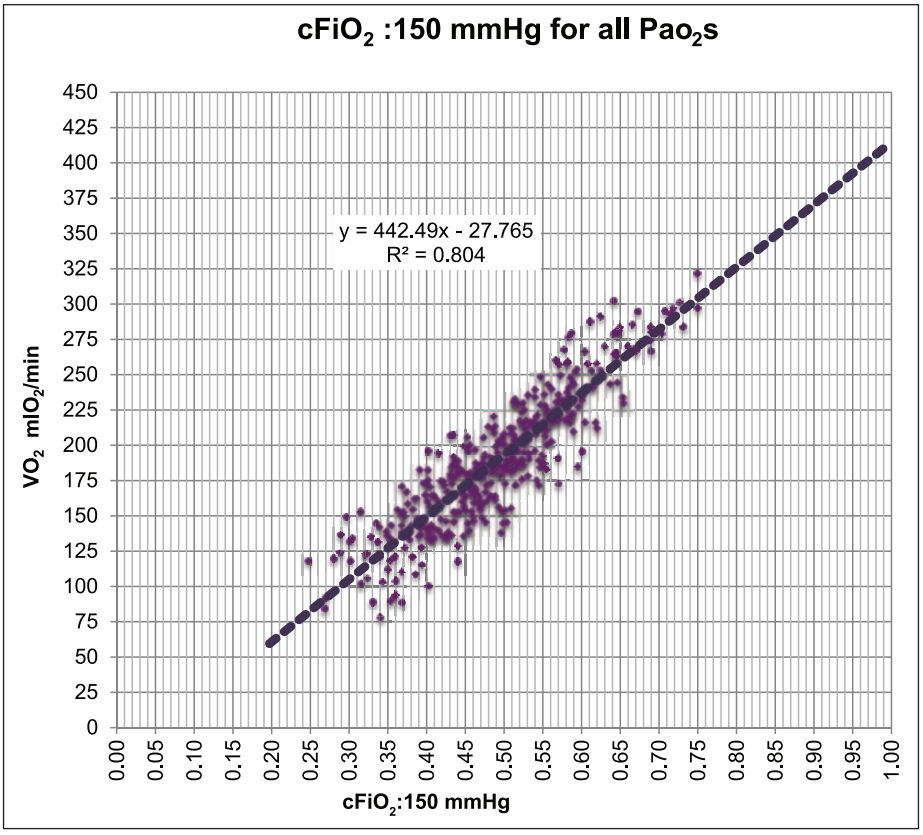

Figure 4. Shows all the VO_2 values from the clinical database versus the $cFiO_2$:150 mmHg.

Not only are the laboratory test results provided by the manufacturer verified on a clinical level, but the knowledge of the predictability of the oxygenator's performance adds to the safe and effective conduct of CPB.[6]

Using this system, other membrane oxygenators can be equally compared, which is more valid then being limited to the maximum blood flow. The perfusionist can assess whether an oxygenator is properly functioning during CPB, especially under extreme or unusual cases and this information may be relayed back to the manufacturer regardless of whether it is negative or positive.

A parameter that is often lacking in our normal routine CPB cases is the calculation of the oxygen indices, which include oxygen delivery (DaO_2), DaO_2 index, VO_2 and VO_2 index. Publications regarding the delivery of oxygen (DaO_2) and changes in VO_2 have shown that it is essential to look at these indices.[7] Using our patient example, we were able to show that the patient was within the normal expected range as far as VO_2 is concerned and that the Medtronic Fusion oxygenator functioned as predicted, which shows it is reproducible and reliable. We also demonstrated that pre-CPB, these oxygen indices may be used as a guideline to set the FiO_2 on a routine basis to attain relatively precise PaO_2s. In essence: it is not only the calculation of the $cFiO_2$, but also incorporating the oxygen indices, which is long overdue in the field of cardiac perfusion.

We aim to achieve a PaO_2 of 150 mmHg during CPB as this allows enough reserve for oxygenation with changes to inlet conditions. However, any PaO_2 may be used by replacing the added FiO_2 value of 0.21 (for a PaO_2 of 150 mmHg) with another number related to the chosen PaO_2.

For example, if a PaO_2 of 200 mmHg is required, this translates into an FaO_2 of 0.28 = 200/713). Therefore, 0.28 would be added to the anoxic fractional difference. For research and analysis purposes, a standard is needed and, therefore, a PaO_2 of 150 mmHg was chosen. When a measured PaO_2 is higher or lower than 150 mmHg, this does not mean that the FiO_2 must be adjusted to the $cFiO_2$ value as CPB is a dynamic process and clinical decisions can be justified. Here, it is important to note that the $cFiO_2$:150 mmHg value is documented and correctly correlated to the VO_2 when the blood gas measurement is made.

The limitations of this evaluation were the characteristic variations in the accuracy of the FiO_2 settings, blood flow, venous saturation monitoring and the blood gas machine calibration. Variations in results can occur when arterial shunts are left open and/or the venous blood in the cardiotomy reservoir is excessively mixed with suction and/or vent blood.

Furthermore, this technique was tested under clinical conditions and, although the statistical correlation within the clinical range is highly significant, the

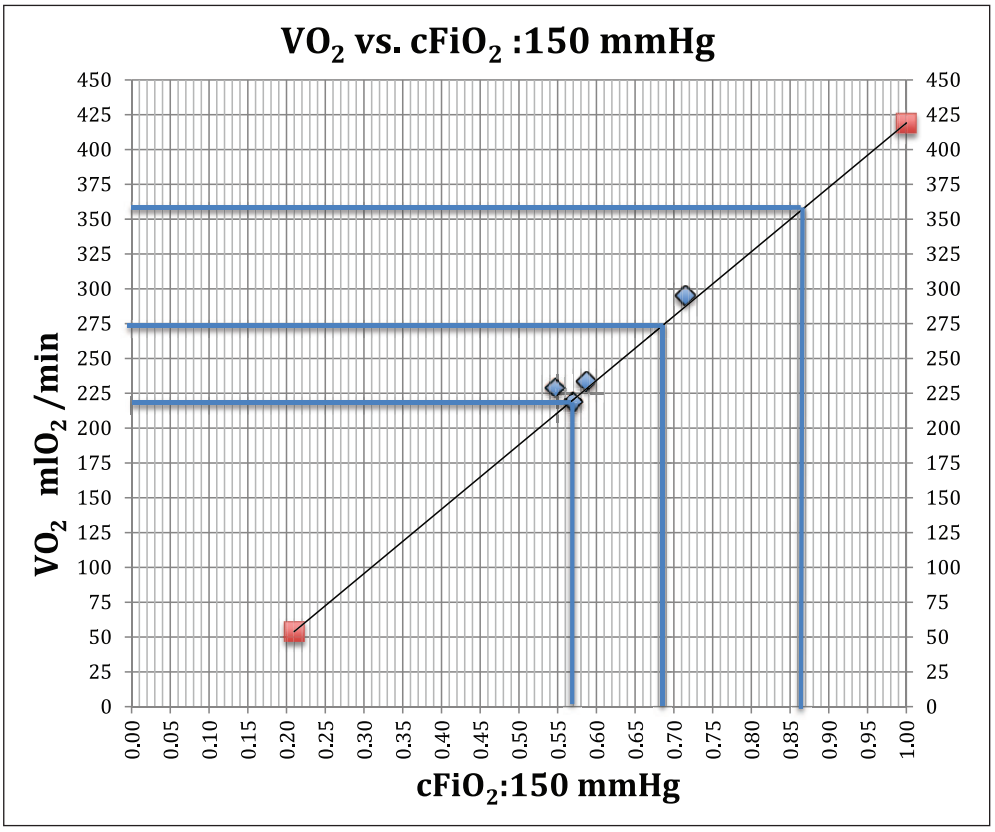

Figure 5. Large patient example (170kg, 179cm, 2.74m^2).
Pre-CPB: Theoretical VO_2 correlated to the $cFiO_2$ (blue lines).
CPB: Actual VO_2 correlated to the $cFiO_2$:150 mmHg (blue diamonds).

extrapolation to extreme values outside of the presented results may differ and is, by nature, an approximation.

Alpha-stat blood gas measurements were used and, therefore, blood gases were not corrected for temperature. The ratio of dissolved and bound O_2 in blood is affected by blood temperature, so it is important to use pO_2 and SO_2 measurements which have not been corrected for temperature.[2]

Temperature correction is controversial and comparison of samples warmed to 37°C were compared to normal results at 37°C, which indicated minute, non-significant changes that further complicate the required calculations.

Conclusion

With the ongoing developments in membrane oxygenator technology, a more useful way of comparing and introducing oxygenator systems is proposed. The ability to measure how effective and reproducible a membrane oxygenator is in regards to O_2T under clinical conditions can offer clinicians and manufacturers a new perspective to improve guidelines to properly evaluate systems. Future laboratory testing to mimic the extreme ends of O_2T will provide the user with much more valuable information.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Appendix 1

Fick Formula:

$$\text{Oxygen Transfer}\left(\text{Oxygen Consumption}\right)\left(\text{ml}O_2 / \text{min}\right) = \left(\text{Hgb} * 1.36 * \left(SaO_2 - SvO_2\right) + \left(paO_2 - pvO_2\right) * 0.03\right) * Q$$

where Hgb is the hemoglobin concentration in gm/L, 1.36 is the Hüfner factor in ml O_2/gm Hgb, SaO_2 is the arterial hemoglobin saturation in decimal form, SvO_2 is the venous hemoglobin saturation in decimal form, PaO_2 is the pressure of oxygen in arterial blood in mmHg and PvO_2 is the pressure of oxygen in the venous blood in mmHg, 0.03 is the amount of oxygen dissolved in the blood in ml O_2/L/min/mmHg pO_2 and Q is the blood flow in L/min.

Modified form may be used during CPB: (Hgb*1.36* blood flow *(1-SvO_2)

Appendix 2: Calculating $cFiO_2$:150 mmHg

Step 1)

Convert PaO_2 into a Fraction (FaO_2) by taking the PaO_2 and dividing this by the barometric pressure (Pb) minus the water vapor pressure of 47 mmHg.

$$PaO_2/(Pb - P_{H_2O})$$

*Pb= Barometric pressure (taken as 760 mmHg).

Step 2)

The FiO_2 minus the FaO_2 gives the anoxic fractional difference.

$$FiO_2 - FaO_2 = \text{anoxic fractional difference}$$

Step 3)

Add 0.21 to the Anoxic Fractional Difference to obtain the $cFiO_2$ to obtain a PaO_2 of 150mmHg.

Final formula: $cFiO_2$: 150 mmHg

$$FiO_2 - (PaO_2/(Pb - P_{H_2O})) + 0.21$$

For ease of use, on the x-axis the $cFiO_2$ is referred to as the "$cFiO_2$:150mmHg" so the standard of using a specific PaO_2 is clearly stated.