Letter to the Editor

It Is Time to Update Membrane Oxygenator Testing Standards and Their Instructions for Use

To the Editor,

Perfusion technology has evolved a great deal over the past 10 years. Heart–lung machines are more customizable. Oxygenators are increasingly including integrated arterial line filtration. Heater–cooler units are more likely to use very low pressure to achieve heat exchanger water flow. Electronic gas blenders (EGBs) are available for precise mixing of oxygenator sweep gas, which is particularly helpful for pH-stat blood gas management. Operations include an increased number of adult congenital heart surgery patients and traditionally pediatric del Nido cardioplegia is being used for adult cardiac surgery patients with acquired cardiovascular disease. The list of advances and changes is long and professional journals are replete with articles describing such. In this letter to the editor, I would like to focus on membrane oxygenator testing standards and their instructions for use (IFU) because I find it not in the best interest of our patients that while perfusion technology has evolved, testing standards and IFUs have not been updated in a meaningful way over the same time period.

V/Q and the Wetted-Out Oxygenator

Traditional perfusion education taught the importance of monitoring ventilation to perfusion (V/Q) ratios during cardiopulmonary bypass (CPB). Most manufacturers formerly, and some today, qualify that clinicians should not exceed a V/Q ratio of 2:1 during CPB. The theory here, at least from what I was taught, is that exceeding this magically even number with microporous membrane oxygenators would increase the chance of pressurizing the gas phase to a point which exceeded the blood phase pressure, which in turn could allow air emboli to enter the patient circuit. Certainly, that should be avoided at all costs! An alternative or perhaps parallel explanation, which is irrefutable, is that oxygenators are tested and validated at precise V/Q ratios by the manufacturer based on data required for submission to the Food and Drug Administration (FDA) to receive approval for use and sale of their oxygenators in the United States. The FDA’s 510(k) requirement specifies that gas transfer data should be obtained at V/Q ratios of .5:1, 1:1, and 2:1 (1). So, those are the ratios tested by manufacturers. This may have worked for many years but with changing technology, particularly oxygenator bundle wrapping technology, I believe the maximum V/Q testing standard should be revisited. In fact, even the Association for the Advancement of Medical Instrumentation and International Organization for Standardization (AAMI/ISO) documents specify that standards must be modified as data and technical progress demands and that this should be reviewed at least every 5 years (2). Many may ask, “Why would a perfusionist need a V/Q ratio in excess of 2:1?” I have two quick answers. First, a high V/Q ratio may be needed to treat an oxygenator suspected of wetting-out. Second, one may be obligated to use a V/Q ratio >2 with the use of an EGB for pediatric patients at low flow rates in whom pH-stat blood gas management is used.

A wetted-out oxygenator may result if water or plasma from the blood phase blocks the micropores of the oxygenator or even leaks into the gas phase itself. This can result in drastically reduced gas exchange performance. Traditional perfusion education recommends increasing the sweep gas flow to maximize gas transfer and to help dry the gas phase out if a device shows signs of failure. That makes sense. What doesn’t make sense is that manufacturer guidance on this critical emergency procedure is so varied or altogether lacking. For example, Sorin specifies that the V/Q ratio should not exceed 4:1 during treatment of a failing oxygenator for two of their oxygenators (3,4). They specify a maximum gas flow rate for three of their devices without mentioning a maximum V/Q ratio (5–7) and for three other devices a maximum V/Q of 2:1 is specified but not in the context of a wetted-out oxygenator (8–10). Terumo does not specify a max V/Q in their IFUs, for normal or emergent use, but their rated gas flow maximum is recommended only for 10 seconds during suspected wet lung and after that brief time period, the IFU explicitly states that the maneuver should not be repeated (11–17). I could not find any Medtronic IFUs that addressed wetting-out of an oxygenator (18–21) and only one which mentioned a maximum V/Q ratio during regular use (21). Certainly, this low-frequency/high-risk-potential CPB emergency deserves well-defined guidance
in all oxygenator manufacturers’ IFU documents. Manufacturers: “Please create a dedicated section in your IFUs, which addresses suspected wet-lung qualifying a maximum gas flow and/or V/Q ratio along with the time frame for this intervention, if applicable.”

**V/Q, EGBs, and pH-Stat at Low Flow Rates**

EGBs, in my opinion, have made clinical practice easier and safer to provide pH-stat blood gas management. Take the Sorin 2 LPM EGB for example. One simply dials in a precise carbon dioxide (CO₂) flow rate and the device delivers, and just as importantly “measures,” the CO₂ flow rate, which is in addition to the oxygen/air flow. The system is simple. It is also safer because the EGB measures actual flow against the set flow to verify that the desired flow is being delivered. In years past, it was difficult to precisely deliver a varied flow of 100% CO₂ with older style low-range flow meters and further complicating matters, in my group’s experience, in-line blood gas monitoring was not as reliable during deep hypothermia, which made precise control of PaCO₂ challenging. The flow in those flow meters varied at times when using very low flow rates and small variations had a big impact on the PaCO₂. In fact, that was one of the reasons Boston Children’s Hospital championed a carbogen delivery system over 20 years ago for pH-stat management (22). Our program transitioned to EGBs in 2015 but it wasn’t without trepidation. The manufacturer maximum V/Q ratio specification was a concern, particularly at low pump flow rates. The best example of this is during regional cerebral perfusion (RCP) on a neonate. At low blood flows, a higher V/Q may be needed to maintain the CO₂ in the normal range. Oftentimes, the CO₂ cannot be turned off since the resulting PaCO₂ would be unacceptably low. For example, if a 3.33-kg neonate is on RCP at 30 mL/kg/min, the blood flow rate is 100 mL/min. The Sorin 2 LPM EGB has a minimum CO₂ flow rate of 20 mL/min. This commonly results in an oxygen/air gas flow rate of 300 mL/min resulting in a V/Q of 3.2 (320/100). We have seen the V/Q ratio as high as 5 during the provision of RCP. EGBs dictate lower limits of oxygen/air gas flow based on the lower limit of CO₂ flow. As mentioned earlier, manufacturer guidance on the maximum V/Q is inconsistent or altogether lacking. Sorin oxygenator IFUs consistently list a max V/Q of 2:1 in their oxygenator IFUs during regular use (3–10). Terumo oxygenator IFUs consistently exclude any mention of a maximum V/Q ratio (11–17). I found one Medtronic oxygenator IFU, which explicitly listed a maximum V/Q of 2:1 (21) whereas their other models make no mention of a maximum (18–20). Certainly, a perfusionist may feel that they are operating an oxygenator within manufacturer specifications if no V/Q is listed in the IFU. But is it safe?

It is time for all oxygenator IFUs to include a maximum safe V/Q ratio and a dedicated section for managing a wetted-out oxygenator. Ideally, an industry-defined and manufacturer-tested maximum V/Q should be included, both for regular use and during treatment of a suspected wetted-out oxygenator. Of course, blood phase pressure will vary and it is an important factor in determining the maximum V/Q. I believe there is an opportunity here for manufacturers to define a new standard of measuring gas phase pressure. Gas phase pressure is normally extremely low. Wouldn’t it be helpful for the perfusionist to know, e.g., that the V/Q ratio for a device would need to be >10:1 before gas phase pressure even becomes a consideration during regular use with a blood phase pressure of 50 or even 100 mmHg? I have never found the oxygenator IFU proclamation, “gas phase pressure should never exceed blood phase pressure,” helpful. More details are warranted. Manufacturers: “Please devise a standard for testing maximum V/Q ratios and specify the maximum V/Q ratio in the IFU. Also, alert us to the conditions where the possibility of gas phase pressure exceeding blood phase pressure is likely in your microporous membrane oxygenator.”

**Oxygenator Heat Exchanger Efficiency Standard**

Perfusionists consider an oxygenator heat exchanger efficiency rating when evaluating a device for possible use in their practice. This performance factor is always reported by the manufacturer and it is commonly in the .4–.65 range (23). Unfortunately, this standardized specification is not qualified at a consistent water flow rate. Sorin tends to use 10 LPM of water flow when creating their IFU heat exchanger performance factor chart (3,4,8,9) though on one device they specify 11.5 LPM (5) and other devices do not have the water flow qualified (6,7,10). Terumo typically uses 15 LPM of water flow (11–17). Medtronic has taken a different approach and specifies heat exchanger “effectiveness” (their term) with multiple water flow rates for some of their devices (19,20), which is actually quite useful, though this is inconsistent across their IFUs (18,21). All perfusionists understand and review an oxygenator’s heat exchanger efficiency rating when evaluating new devices for their practice. Most importantly, perfusionists trial a device under varied clinical conditions to ensure it meets their needs. Clinical trials at one’s own institution are of course the gold standard. But, wouldn’t it also be helpful if manufacturers used standardized testing conditions for heat exchanger water flow when reporting their efficiency rating? Oxygenator heat exchanger testing needs to be standardized with clinically relevant water flow rates to allow users to objectively compare performance (24). It is also worth mentioning that the heat-exchange performance factor and HCU water flow rates may see increased attention as cardiac surgery programs consider the location of the HCU in, or out of, the operating room considering the risk of surgical infection heater–cooler units themselves may pose (25). Granted,
whether a manufacturer utilizes 10 LPM vs. 11.5 LPM of water flow during testing may not result in a clinically significant variance but the bigger question is “What is the downside of standardizing a test, which clinicians regularly use to evaluate equipment?” Manufacturers: “Please standardize heat exchanger efficiency testing with a clinically relevant set of water flow rates, perhaps 8, 10, and 15 LPM.”

Oxygenator Heat Exchanger Testing Prior to Clinical Use

All manufacturers state in their membrane oxygenator IFU that the heat exchanger integrity must be tested prior to use by circulating water through the heat exchanger. Sorin recommends water circulation for “a few minutes” (3–10). Terumo recommends water circulation for at least 5 minutes (11–17). Medtronic recommends a water test but does not specify a time requirement (18–21). Testing the heat exchanger integrity is a sound clinical practice, and most perfusionists adhere to this recommendation. It is important to note that water testing specifications were developed at a time when the HCU provided water flow with higher positive pressure in the water system. Most HCU today deliver water flow under very low pressure, which intuitively is safer since any defect in the water–blood barrier would more likely result in a blood-to-water leak as opposed to the more dangerous water-to-blood leak. Traditional positive pressure water testing has been shown in at least one case report to have limitations (26). Furthermore, using air pressure to test the heat exchanger integrity has been shown to be effective in detecting defects (27). My perfusion team normally utilizes traditional positive pressure to water test oxygenators on a custom pressure–regulated system in our pump room but are considering the air pressure test. However, we have trepidation moving to this method. First off, the air pressure test is not sanctioned by the oxygenator manufacturers. Moreover, oxygenator manufacturer IFUs by and large do not address the possibility of a static electricity discharge across an oxygenator bundle or heat exchanger, which could compromise the integrity of either component resulting in a leak. This phenomenon was nicely summarized by Snijders et al. in a 1999 Perfusion article (28). In fact, only the IFU for the Sorin Inspire series qualifies that the heat exchanger water lines must be attached with water running through polyvinyl chloride (PVC) pump headers are in use to prevent the risk of static electricity discharge within the oxygenator (5). Manufacturer IFUs always list water testing prior to the priming procedure, but it is not explicitly stated that priming may only commence with water circulating through the heat exchanger. This deserves to be further elucidated for the user if a manufacturer concludes that there is risk to the membrane bundle or heat exchanger if the unit is primed without water circulating through the heat exchanger, particularly if PVC tubing is in use. Manufacturers: “Please specify in oxygenator IFUs that in order for water testing to be effective, it must be done in a positive pressure system and specify the pressure which should be used. Please also investigate whether an air pressure testing method for heat exchanger integrity can be recommended. Finally, please be explicit about the conditions which risk a static electricity discharge in your devices.”

The FDA 510(k) specifications and the AAMI/ISO oxygenator testing standards have been revised over the past 30 years yet we still lack standards for all specifications the perfusionist is interested in when evaluating an oxygenator and its heat exchanger (1,2,29–31). This makes objective comparisons unnecessarily difficult. A 1996 editorial in Artificial Organs pointed out that as oxygenator membranes evolve, testing methods should as well (32). That was 20 years ago! Certainly, the evolution of perfusion technology and techniques warrants updating and standardizing the specifications I addressed in this letter to the editor.

In closing, I would like to point out that oxygenator manufacturer IFUs commonly state that when defects in the heat exchanger or device itself are detected, the device should be discarded or simply not used. Wouldn’t it be the best interest of the patient populations we serve if instead manufacturers explicitly specified in the IFU how the device should be packaged for return and properly reported to the FDA? Defective equipment from a medical device manufacturer should always be returned and investigated to ensure product-line safety and to verify that a manufacturing lot issue does not exist (33). If an issue does exist and is identified, it may prevent harm to a patient! Finally, as healthcare professionals we must all, “First, do no harm.” Let’s strive to eliminate unnecessary variations in oxygenator testing standards and work to have oxygenator IFUs include more useful information for the practicing perfusionist.

Gregory S. Matte, CCP, LP, FPP Co-Chief/ Clinical Coordinator for Perfusion Boston Children’s Hospital Boston, Massachusetts

REFERENCES

MEMBRANE OXYGENATOR TESTING STANDARDS AND THEIR INSTRUCTIONS FOR USE