Invited Editorial

Understanding Off-Label Use and Reference Blood Flows in Modern Membrane Oxygenators

Gerard J. Myers, RT, CCP (Emeritus)

Eastern Perfusion International Halifax, Nova Scotia, Canada

Abstract: This editorial will address two issues that are still a source of global controversy and confusion in present day perfusion practice. Membrane oxygenators are designed and tested to a set of stringent flow standards prior to their release from every manufacturer. But how well do we know the iatrogenic consequences of pushing these devices beyond their maximum rated limits? In addition, how well do we know the meaning of the term ‘AAMI Reference Flow’ as it relates to the Manufacturers Maximum Rated Flow? Keywords: off-label, reference blood flow, oxygenator, gaseous microemboli, acute kidney injury, AAMI.

The off-label use of medical devices is an issue that has been around for many years. In the Journal of Law, Medicine and Ethics, Dresser et al. (1) stated that off-label prescribing is an integral part of contemporary medicine. Many patients benefit when they receive drugs or devices under circumstances not specified on the label approved by the U.S. Food and Drug Administration. However, they also stated that off-label prescribing can also harm patients and that the potential for harm is greatest when the off-label use lacks a solid evidence basis.

The National Task Force on CME Provider/Industry Collaboration’s Fact Sheet (2) examines the use of off-label medical devices and discusses the issues and statistics around this seemingly common practice. However, the point that is clear in the task force statement is that off-label use of a medical device should contain scientific evidence that the off-label use provides a clinical advantage...the same point that is made by Dresser et al. (1). In other words, we should have sound evidence-based reasons for pushing an oxygenator (off-label) during extracorporeal circulation and, more importantly, that it has minimal risks for the patient and their postoperative outcomes. Herein we find the major issue with pushing membrane oxygenators beyond their Manufacturer’s Rated Flow (sometimes referred to as Maximum Rated Flow).

Off-label use of small adult oxygenators is often only based on the opinions of the clinician or the assumptions of reduced transfusion statistics solely based on very small reductions in prime volume. The practice of pushing oxygenators above their rated flows probably began in pediatric oxygenators, long before they were done in small adult oxygenators. From my own clinical perspective, it was more or less a way to show a particular oxygenator had enough gas transfer to handle larger patients, and I could save some priming volume in the process.

However, it is difficult to demonstrate the true hemodilution benefits of off-label use with small adult oxygenators, especially when there are so many other contributors to fluid administration during the course of cardiac surgery. When it comes to choosing an undersized oxygenator for bypass, we have to be aware of the things we cannot see or rarely measure, like increasing the risks for gaseous microemboli (GME) morbidity by adversely affecting the patient’s endothelial network and potential outcomes.

One thing we do know, that is evidence-based, is the fact that as we approach/exceed the flow rate of an oxygenator’s manufacturer-rated flow, the amount of postarterial filter GME increases for many oxygenators (3–6). It is also a well-known fact that GME increase patient
morbidity by causing/contributing to glycocalyx disruption, endothelial damage, inflammation, edema, and blood-brain barrier dysfunction, all of which ultimately leads to fluid extravasation, platelet and white cell activation, release of proinflammatory cytokines, and cellular damage (7–11). The only uncertainty regarding GME during cardiopulmonary bypass is whether they are the only source of all postoperative neurocognitive dysfunction or whether they are just another contributing factor to the dysfunction along with other comorbidities such as age, surgery, anesthesia, cerebral hypotension, and solid emboli (12). In either case, the evidence indicates that as the unique practitioners of cardiopulmonary bypass, we need to use every means to reduce or eliminate GME during cardiopulmonary bypass, even if there are other potential contributing factors. To that end, tremendous strides have been undertaken to achieve this goal over the past decade.

As perfusionists, we are all well aware that our ethical objective as clinical practitioners in cardiac surgery has always been to reduce or eliminate all sources of potential harm to our patients, certainly not replace one source of harm with another source of harm. It makes no logical sense that we would risk the potential of increasing harm to an individual’s vascular physiology (and blood–brain barrier) just because we can save small amounts of priming volume in an adult patient by undersizing an oxygenator.

The implied benefits (decreased allogeneic transfusion) of using one volume reduction action (saving 100–120 mL) by pushing small adult oxygenators above their manufacturer-rated flows, while at the same time using numerous other perioperative decisions not to transfuse, sends a potentially misguided message to clinicians. That message is...if one were not to save 100–120 mL of prime volume in an adult patient by using an oxygenator off label, that patient would have suffered the consequences of an allogeneic transfusion because of that inaction. Using appropriately sized oxygenators for prime volume reduction in small adult patients is a more reasonable approach to excessive hemodilution and avoids the issues of increasing GME morbidity (13–16). However, common sense has to tell us that it is extremely difficult, if not impossible, to correlate the saving of 100–120 mL of crystalloid (the equivalent of a 4-ounce glass of water) in an adult patient to a reduction in allogeneic blood transfusions when you have so many other perioperative variables that influence hemodilution as well. To do this, one would have to measure and control all volume infusions, volume outputs, blood losses, and medical decisions to transfuse throughout the entire perioperative stay, using only the 100–120 mL as the single variable change.

Excessive hemodilution is an independent risk factor for transfusion, but it is a manageable (or modifiable) risk factor. There are many ways to safely and effectively manage excessive hemodilution without pushing small adult oxygenators above their manufacturer-rated flows. Some of these methods can be done by perfusionists alone, whereas others require the cooperation and education of the other members of the perioperative team. Other than addressing the priming volumes of oxygenators, filters, and circuits, some other ways to address excessive hemodilution are:

1) consider the type of hard-shell venous reservoir used. Some venous reservoirs have minimum operating levels of 300 mL, whereas others have minimum operating levels of 150 mL. In addition, hold-up volumes while priming or during cardiopulmonary bypass (CPB) can range between 10 mL and 205 mL, depending on the reservoir. Both of the latter designs can impact the clinician’s ability to avoid adding extra operating volume during CPB (17);

2) identifying and treating anemic patients (iron, erythropoietin) during the preoperative assessment period to eliminate the potential of those individuals arriving for cardiac surgery in a state of anemia, which is an independent risk factor for transfusion (18);

3) removing the impact of excessive volumes of fluid (crystalloid/colloid) before going on bypass by eliminating the volume-loading practice of anesthesia during induction and reducing the lengths of the arterial and venous tubing used for CPB (19);

4) using retro autologous priming (RAP) and venous antegrade priming (VAP) on all patients, not just the small body-weight patients and Jehovah Witness patients. This technique is simple, easy to implement, and, with the cooperation of anesthesia, can be a contributing factor to reduce hemodilution. It is totally illogical to choose an oxygenator that has 100 mL less prime volume over another and then decide not to useRAP/VAP, which can reduce prime volumes by 400–900 mL (20);

5) review and reduce the frequency and volume of blood sampling during the entire perioperative period (including the intensive care unit) to prevent iatrogenic blood loss. Studies have shown that the amount of blood lost from sampling alone can be as much as 1–2 units of whole blood over the period of only a few days (21);

6) although the surgeon makes the ultimate decision on cardioplegia, consider the type of cardioplegia as a variable hemodilution factor (for example, it takes 5 L of 4:1 blood cardioplegia and 200 L of Quest microplegia to equal the same intravascular hemodilution effects as 1 L of crystalloid cardioplegia);

7) discarding sequestered suction blood leads to the loss of red cells, proteins, platelets, and other clotting factors and may lead to postoperative transfusion. Do not make a unilateral decision to discard this blood at the end of the case, regardless of the patient’s nadir
hemoglobin/hematocrit. Instead wash it with an auto-
transfusion machine or run it through a lipid type of
filter before reinfusion to the patient; 8) use a hemoconcentrator in all extracorporeal circuits
to maintain fluid balance throughout bypass, control
hyponatremia, and hemoconcentrate extracorporeal cir-
cuit blood volume after termination of bypass. Hemocon-
centration is a powerful tool and can lead to a state of
postoperative dehydration if used excessively; and
9) be aware that colloids will hemodilute the intravascular
space more than crystalloids will; it is purely the nature
of their composition. All intravenous fluids are drugs
with their own side effects, including their own indica-
tions and contraindications to treat the various volume
states of patients coming for surgery. Patients presenting
for cardiac surgery are in one of three volume states on
their operative day...dehydrated (reduced extravascular
volume with; serum sodium levels >150 mmol/L, or
serum osmolality >300 mOs mol/L), hypovolemic
(reduced intravascular volume), or hypervolemic
(increased intravascular and extravascular volume). The
primes an adult program uses should not just be simply
be either a crystalloid prime or a colloid prime...if
possible; they should be individualized primes to address
the patient’s volume state when they arrive on their day
of surgery [For example, patients who are dehydrated
are best treated with crystalloids to replenish their extra-
vascular losses, whereas hypovolemic patients are best
treated with colloids to replenish their intravascular
losses] (19,22).

The AmSECT Standards and Guidelines for Perfusion
Practice (23) state that every means should be used to
reduce hemodilution. ...but I am certain they also meant
that this should not be done at the risk of increasing mor-
bid events in other areas of the extracorporeal circulation
at the same time. If we accept the fact that GME are a
morbid event during CPB, then we must also accept the
fact that if we intentionally increase GME by undersizing
oxygenators, we are increasing morbidity to that patient.

Sometimes the pressures perfusionists face from the
medical community to show evidence of reducing even
small amounts of prime volume is insurmountable and
often forces clinicians to question the obvious and defend
the risky. However, the practice of intentionally pushing
an oxygenator beyond its Manufacturer-Rated Flow should
not be encouraged in the name of challenging the manufac-
turer instructions for use (IFU) or improving transfusion
statistics by saving 100–120 mL of prime volume. The mere
implication that a program can improve their transfusion
statistics simply by using oxygenators in an off-label manner
entices others to do the same.

The International Standards Organization (ISO) is a
worldwide federation of national standards bodies, which
include many organizations such as the Association for
the Advancement of Medical Instrumentation (AAMI)
and the American National Standards Institute (ANSI).
Therefore, the American Standard (ANSI/AAMI/ISO
7199:2009) suggested policies are identical in there recom-
end standards for blood gas exchange devices or oxygen-
ators (23). AAMI standards are recommended practices,
technical information reports, and other types of technical
documents that are developed by AAMI and are there-
after considered voluntary standards; their application is
solely within the discretion and professional judgment of
the user of the document (the manufacturer) (24). There is
a broad misunderstanding of the meaning of the term
AAMI Reference Flows within the global perfusion
community, and unfortunately these flows are some-
times listed just below the Manufacturer’s Rated Flow on
the IFU sheet.

In regard to Manufacturer Rated Flows, all oxygenators
are tested and rated for clinical flows that are established
by achieving ISO/AAMI standards for oxygen transfer,
carbon dioxide transfer, electrolytes, hemolysis, and plate-
let function. In addition to this are the individual manufac-
turers’ GME, pressure drop, and prevention of reservoir
outlet vortexing standards that are decided and tested by
each oxygenator manufacturer. Before any of these tests
reach unacceptable levels during testing, the oxygenator’s
maximum rated blood flow is established by the manufac-
turer. After this, all manufacturers place the Manufacturer
Rated Flows (MRF) in their IFU and this flow is now
considered the labeled use for that device. The devices
are then marketed around the globe with their labeled
use designation. Without in vitro testing and the MRF
designation, all manufacturers would just sell several-sized
membrane oxygenators and let perfusionists decide what
flows to use at.

The AAMI Standard Reference Blood Flow (ASRBF)
was initially placed on most pediatric and small adult
membrane oxygenator IFUs when those membranes first
came into the market many years ago as an indicator of
gas transfer capability. Since that time, most manufac-
turers have removed the ASRBF from their small adult
oxygenator IFUs because it appears that it was simply
a constant source of confusion for perfusionists. For
example, when the MRF is 5.0 LPM in the IFU, and the
AAMI Standard Reference Flow is stated to be 7.0 LPM
in the same IFU, clinicians assume that the device could
be used up to 7.0 LPM during routine bypass (25).
The AAMI Standard Reference Flows are calculated
values for oxygen transfer only and are not intended to
replace the manufacturer’s maximum rated blood flow.
This AAMI reference blood flow is the flow at which
oxygen delivery in that device does not drop below 45 mL
O₂/min/L of blood flow using AAMI standard conditions
(35% hematocrit, 37°C, hemoglobin 12 mg/dL, FiO₂ = 100%).
The value is derived by plotting a graph using increasing flow rates obtained from establishing the MRFs. At the highest plotted flow rate that is able to provide at least 45 mL O₂/min/L blood flow, the AAMI Reference Blood Flow Rate is established. It is intended to demonstrate to the user that if necessary, that reference flow rate would provide a minimum oxygen transfer of 45 mL O₂/min and carbon dioxide transfer of 38 mL CO₂/min.

However, the AAMI Reference Flow Rate is not in the IFU of any adult oxygenator. This may be the result of the fact that the IFU would probably have to indicate an AAMI Standard Reference Flows in excess of 9 or 10 LPM for these adult oxygenators. So the question should be...why is it only printed on the IFUs of some small adult and pediatric oxygenators?

Finally, the practice of pushing an oxygenator above its manufacturer-rated flow could eventually put perfusionists on a direct collision course with true progress, like that demonstrated by works of Ranucci (26) and DeSomer (27). Their evidence-based findings are based on the renal advantages of increasing blood flows above our standard 2.4 L/m²/min (but only if needed) when facing clinical situations like progressing anemia, hyperlactatemia and decreasing saturations. The authors found that keeping the oxygen delivery in blood >262 mL/min/m² may lead to better renal perfusion and reductions in the incidence of postoperative acute kidney injury (AKI) during hemodilutional CPB. However, using an undersized oxygenator beyond its maximum rated blood flow dramatically reduces the perfusionist’s ability to respond to an ever changing environment of increasing oxygen demands, progressing dilutional anemia, and development of hyperlactatemia. In the latter situation, off-label use of an oxygenator has the potential to place patients at risk for iatrogenic injury and AKI in addition to the previously mentioned GME consequences.

The pressures perfusionists face to reduce hemodilution are immense and often interfere with simple common sense and a total view of choosing the most effective oxygenator design for each patient that will not only minimize hemodilution...but reduce GME, meet the unexpected metabolic demands of our patients, and still keep within the boundaries of patient safety. This cannot be done if we are compelled to focus entirely on the small reductions in prime and ignore the potential for microemboli morbidity and the consequences for undersizing oxygenators in an ever changing perioperative environment.

I fear we are constantly pushing the limits of devices in a clinical setting and are often forced to look the other way in our goal to decrease every milliliter of fluid used during bypass. Medical practitioners complicate this issue because they demand and expect perfusionists to give them volume-reducing compliance without being aware of the consequences perfusionists face when pushing oxygenators beyond their limits. Perhaps it is the perfusionist’s responsibility to educate the medical community regarding the use of undersized oxygenators and their potential influence on patient safety.

What should be addressed even more than reducing small increments in priming volume is the entire perioperative team’s understanding and cooperation in their quest to reduce perioperative hemodilution. To meet such a goal, a program needs to address such things as anesthesia volume loading, excessive perioperative blood sampling, excessive perioperative colloid use, preoperative anemia, program history, transfusion triggers, type of cardioplegia, perfusion intraoperative volume management, and more liberal use of hemoconcentrators and autotransfusion devices...keeping in mind any potential iatrogenic risks associated with changing clinical practice. Hemodilution during cardiac surgery is certainly not an individual sport...but it is a team sport.

Understanding and using manufacturer IFUs to guide us in our clinical practice should never replace a professional’s clinical judgment, but at the same time, they should not be taken for granted and challenged in a clinical scenario without fully understanding the IFUs and any potential negative implications to our patient population. It is the willingness to explore all infusion models and modify transfusion protocols by the “entire cardiac team” that changes transfusion statistics, not undersizing membrane oxygenators by using them in an off-label manner during CPB.

REFERENCES