Is it Time for Goal-Directed Therapy in Perfusion

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Thank you, Ben. I appreciate the opportunity to speak today and be part of this symposium. I do not have any relationships, financial or other conflicts of interest related to this topic, however, I do want to disclose that I am the default speaker or “weakest link” on this program today. Six months ago, when Ben and I started to talk about this session, we had a “dream team” of speakers in mind for this session. And we were able to deliver all of them today except one. Dr. Filip de Somer had planned on being here, but several weeks ago, we learned that he would not be able to attend and I am a substitute for him today. I’ll be presenting on goal-directed therapy and reviewing two important papers on that topic, one authored by Filip. I also acknowledge the work of John St. Onge from Maine Medical Center. John leads our efforts related to goal-directed therapy and it is his effort that has secured our ability to measure goal-directed perfusion (GDP) parameters at our center and he is the thought leader at our center on GDP.

My aim today is to use the audience response system (ARS) to gain some context knowledge on practices of those represent in this room, specifically the things that you measure to determine adequacy of perfusion. I will review several key historic references on adequacy of perfusion. But for the most part, I will review two landmark GDP studies, one from Marco Ranucci published in the Annals of Thoracic Surgery in 2005 (1) and the second by de Somer published in Critical Care Medicine in 2011 (2). These two studies have been important catalysts to the growing interest in goal-directed therapy during cardiopulmonary bypass. Finally, I will share practical applications of this concept that we’re using at my center.

So here is an ARS question. Do you measure venous oxygen saturation levels during cardiopulmonary bypass continuously, intermittently, or do not measure (Figure 1)?

Okay. That’s not too surprising. The majority of us are using an inline monitor to monitor the venous saturation during bypass.

And here’s the next question. Do you routinely measure carbon dioxide production index (VCO₂ index; Figure 2)? This is measured at the exhaust for the oxygenator. Studies have shown that it is a good parameter related to metabolic requirement.

It appears that 90% of those of us in this room do not use that technology.

Do you routinely measure venous PO₂ levels during adult cardiopulmonary bypass (Figure 3)?

All right. Thank you. That technology is available continuously. It’s interesting that a third of us don’t measure venous partial pressures of oxygen. Early studies looked at venous PO₂ and arterial to venous PO₂ differences, as a measure of adequacy of perfusion.

The next question, is about routine measurement of serum lactate levels during cardiopulmonary bypass (CPB) in your adult patients (Figure 4).

It is apparent that more than half of us are not measuring lactates routinely in adult patients. I suspect that lactate measurement is more routinely measured for pediatric patients. You know, one of the studies that Dr. Rivers referred to was by Demers and colleagues, which showed that the critical level seems to be greater than 4 mmol/L, where there’s a sharp increase in mortality and morbidity in patients that experience a lactate greater than—greater than four during cardiopulmonary bypass (3). Professor Ranucci also looked at metabolism and anaerobic metabolism during bypass and how that relates to oxygen delivery. And in this paper published in 2006, he showed that 260 mL/min/m² seems to be a critical level of oxygen delivery where lactate increases and anaerobic metabolism is quite substantial (4).
Dr. Rivers shared with us this from his work from 2001 that looking at early goal-directed therapy, that by changing the way you manage patients, as he—as he told us by having early goal-directed therapy and moving from a situation where you treat hypotension and use fluid resuscitation to one where you use aggressive measures and measure oxygen delivery, improve cardiac output, and have this approach where you use a number of therapies and monitor a number of areas that you can improve outcomes. And in that early work, they showed a reduction in mortality from 46% to 30% in septic shock patients. And as he told us this morning, now that’s for patients in septic shock. Now 15 years later, septic shock patients have less than a 20% mortality.

If you look in our literature, some of the earliest thinking and some of the earliest work on adequacy of perfusion are in Pierre Galletti’s book published in 1962 (5). And an interesting statement in that book, and there page after page of work looking at the effects of hypothermia, looking at what flow rate is an adequate flow rate, what should be measured to determine accuracy of perfusion. And it’s summarized in this statement in the book that, “It appears that during periods of decreased oxygen supply, the perfused organism that is partly under an anaerobic condition that—and incurs an oxygen debt which must be paid back at a later time. As long as energy expenditures does not fall below metabolism of preservation, the organism can be fully revived.” The excerpt from this early text book begs the question: how well are we monitoring oxygen delivery and assessing the delivery of oxygen to cells and how often do we fall below the critical level of delivery?

The landmark paper written by Marco Ranucci, a retrospectively, studied acute kidney failure after coronary operations. Other investigators, at that time, were looking at low hematocrit and its association with mortality, low output failure, and renal injury. Ranucci and his team sought to exam delivery that brings both hemoglobin level and cardiac output or CPB blood flow into the equation. Oxygen delivery could be improved through either transfusion or increasing cardiac output. Potentially, the two actionable conditions that might be considered to mitigate the occurrence of acute kidney injury (AKI). Their study included 1,040 consecutive patients that had undergone coronary artery bypass graft procedures, examining the association of nadir hematocrit, nadir pump flow, and nadir oxygen delivery. The primary outcomes investigated were creatinine levels and the AKI rate. They did find that several preoperative variables, specifically, age, baseline creatinine, and chronic obstructive pulmonary disease, were associated with an increased rate of AKI and an increase in creatinine. The lowest hematocrit and the nadir oxygen delivery in those 1,040 patients were associated with higher levels of postoperative creatinine and higher rates of AKI, defined as the need for renal replacement therapy, so really severe injury to the kidneys. They found that low DO$_2$ was the best predictor for AKI and high creatinine and low hematocrit after adjustment for transfusion were also predictive. This was a great contribution; however, there are weaknesses in this study. One weakness was that they only measured the nadir levels of those parameters. They did not
measure the duration of exposure to low delivery or low hematocrit. Another weakness of the study was that they did not look at subtle kidney injury, rather only the patients requiring renal replacement therapy. Future studies looking at these two areas might further reveal a dose-related nature of reduced oxygen delivery on kidney injury.

To summarize, Ranucci found that low oxygen delivery index (273 mL/min/m²) was associated with severe AKI and increases in serum creatinine. They calculated receiver operator curves (ROCs) and found that low DO₂ was the most sensitive and specific measure, followed by hematocrit level and blood flow rate during CPB.

A second important multicenter study conducted by Filip de Somer with Ranucci as a co-investigator, took this concept a little further by including carbon dioxide production during cardiopulmonary bypass and a more sensitive definition of AKI. They used the AKI Network (AKIN) definition for AKIN 1 and 2 levels where increase in creatinine to between 150 and 200% increase from baseline is considered stage one, 201–300% stage II, and >300% stage III (6). They also used multivariate logistic regression to get a better understanding of what exposures were associated with kidney injury and increased creatinine. They found that a Nadir DO₂ less than 262, very similar to what was shown by Dr. Ranucci’s group, was associated with AKI odds ratios of 3:1. Furthermore, they found that when the DO₂/VCO₂ index was less than 5.3 that this was also of predictive of AKI. They also reported that nadir DO₂ was associated with increased intensive care unit length of stay. De Somer and colleagues proposed that GDP, aimed at preserving DO₂ should be tested as a preemptive strategy to reduce the occurrence of postoperative AKI. They also, looked at the sensitivity and specificity of these exposures and found low DO₂ to be the most predictive measurement, followed by the ratio of DO₂ to VCO₂ and then the nadir hematocrit ranked third in sensitivity and specificity.

So what are some practical ways we can apply these principles to practice? At Maine Medical Center, we use a tool to estimate DO₂ during bypass and an algorithm that provided an estimate of the minimal required blood flow for a specific patient under certain conditions (Figure 5). We have incorporated this into our care plan where we calculate an estimated DO₂ for a specific patient based on hematocrit.

We enter patient parameters including; the procedure, the patient’s age, but most importantly, height, weight, and hematocrit. The sheet calculates an estimated hematocrit on bypass and can predicts the hematocrit should various blood conservation procedures such as retrograde and antegrade autologous priming or should transfusion of blood into the CPB circuit is done prior to CPB. The shaded section on the sheet is a “look up” table that

Figure 5. Maine Medical Center CarePlan—parameters in red are entered into the spreadsheet. Parameters in blue are calculated. The table in the shaded box is a lookup that estimates the flow rate required to maintain a DO₂i > 273 mL/min/m² over a range of hematocrit levels for a specific patient.
approximates the flow needed at various hematocrits to maintain a $\text{DO}_2 > 273 \text{ mL/min/m}^2$.

Since July 2014, we’ve been using the CONNECT electronic charting system from LivaNova (Houston, TX). The CONNECT system has a feature for capturing and quantifying GDP parameters (Figures 6 and 7).

For example, the GDP monitor provides you a continuous measurement of oxygen delivery, oxygen consumption, and carbon dioxide production and respective calculated ratios. We have not implemented carbon dioxide measurement at our center, since we use carbon dioxide to flood the surgical field, which confounds the accuracy of carbon dioxide measurement.

So during a procedure, using the monitor, the perfusionist can follow continuously the oxygen delivery and can have an idea of how well that goal is being met for a particular patient. If the oxygen delivery is low, changes can be made in the flow rate or communication can occur with the surgical team about checking cannula position or about looking at how the heart is being retracted or other factors influencing venous drainage or blood flow rate.

This system has the capability of quantifying variation that occurs during CPB. Quality indicators may be selected. We have selected mean arterial temperature, mixed venous oxygen saturation, perfusion temperature, oxygen delivery index, the ratio of delivery to carbon dioxide production, hematocrit, and cardiac index and we have set thresholds for each parameter. The system will quantify the number of minutes of variation that occurs during cardiopulmonary bypass and calculate quality scores (percentage of time within range as shown in Figure 7).

The Quality Scores in Figure 7 shows the minutes of variation where values were below the preset threshold. It tells you what the bypass time is and what percent of the case you’ve been within the threshold. The Quality Scores tab can be opened during a procedure to obtain the amount of unwanted variation during a particular procedure. At our center, we have begun to record the total variation for each of these parameters in our perfusion registry form.

For each patient record, in addition to collecting patient demographic data and outcome data, we record these values. This information may be used to study the relationship between minutes of variation and patient outcomes.

One of the surprising things we learned from this group of 183 patients was the frequency and duration of low $\text{DO}_2 < 270 \text{ mL/min/m}^2$ threshold. We learned that the minutes of variation were substantial and that we had opportunity to improve. And there was an association in the more minutes of exposure, the more minutes of low $\text{DO}_2$—the higher the rate of AKI in patients in that tercile that had the most exposure (Figure 8).

<table>
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<th>Parameter</th>
<th>MAP</th>
<th>$\text{S}_\text{O}_2$</th>
<th>$\text{T}_{\text{PaCO}_2}$</th>
<th>$\text{DO}_2$</th>
<th>$\text{VO}_2/\text{DO}_2$</th>
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Figure 7. Quality Scores from the CONNECT System LivaNova.
The Northern New England Cardiovascular Disease Study Group, our registry research group, was one of the first study groups to recognize the relationship between duration of AKI and long-term outcomes. In 2009, work lead by Jeremiah Brown, an epidemiologist, and Robert Kramer, a cardiac surgeon in our research group, reported that the duration of the patient’s high creatinine was associated with long-term survival. For patients with no AKI (7), there was about an 80% survival at 5 years. However, if the creatinine was elevated for 1 day, the 5 year survival was worse. If the creatinine remained elevated for 3–5 days 5-year survival was even worse. If the creatinine was elevated for more than 7 days, and then more than half of those patients weren’t around in 5 years.

So from that study, the long-term implications of AKI compel us to urgently seek changes of processes of care that will improve postoperative kidney function and long-term survival.

We have a 60-patient pilot study underway that focuses on patients that have a high risk of postoperative AKI. The aim of the study is to determine if monitoring GDP parameters and rapidly correcting low oxygen delivery within minutes of onset, we can reduce the rate of AKI for this high-risk group. This change may guide the timing of red blood cell transfusions. At our program, of those patients that get RBCs, about 72% get them in the critical care unit. Perhaps, starting some of these transfusions earlier or implementing other interventions to correct low DO₂i during CPB will result better patient outcomes.

So is it time for goal-directed therapy in perfusion? My prediction is that time will tell. But it’s very encouraging what we’re seeing in the literature these days in the increased interest in measuring specific goals in an effort to try to improve outcomes for patients. Thank you.

REFERENCES