

## Lecture

# *Oxygen Pressure Field Theory, The Krogh Cylinder and Long-Term Extracorporeal Perfusion: An Old Concept Provides New Insight*

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### ABSTRACT

This article describes oxygen pressure field theory and its relevance to the application of long-term perfusion support. Prolonged applications of extracorporeal support for cardiac or pulmonary failure require a more perceptive understanding of perfusion and how it works over a period of days or weeks. The key to this understanding lies in the concepts of the Krogh tissue cylinder, the lethal corner and perfused capillary density. The interrelationships of these concepts define the microvascular redistribution system and its need to remain in balance in order to maintain homeostasis. An imbalance in any of the aspects described could result in tissue damage and eventual death.

Perfusionists attempting to perform long-term extracorporeal support can improve the odds for patient survival with a clear understanding of oxygen pressure field theory and its associated concepts. By maintaining a balance in the microvascular redistribution system, the perfusionist not only keeps the patient alive, but creates an environment where healing can occur over a period of days or weeks.

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## INTRODUCTION

Extracorporeal perfusion applications are rapidly expanding (1-3). Perfusionists are increasingly applying themselves to the challenges of long-term support in the intensive care unit (ICU) (4-8). Because of this there needs to be a greater understanding of perfusion and how extracorporeal support works over a period of days and weeks. For example, in the operating room, a patient who develops a base deficit on bypass which accumulates at the rate of 1 milliequivalent per liter (mEq/L) per hour is not in very serious trouble. The perfusionist may not even choose to treat such a minor deficit if all other parameters are within accepted normal ranges (9), knowing that the procedure will end in a few minutes or hours. But, in the ICU, a patient may be on some type of extracorporeal support which, prospectively, will last for days, if not weeks. If such a patient develops an insidious base deficit which increases at the rate of 1 mEq/L per hour, he or she will most likely die in less than a day, even if bicarbonate is administered. This is because the LD 50 (the level at which 50% of the patients die) for base deficit is about 19 mEq/L. The patient would reach that point in about 19 hours (10).

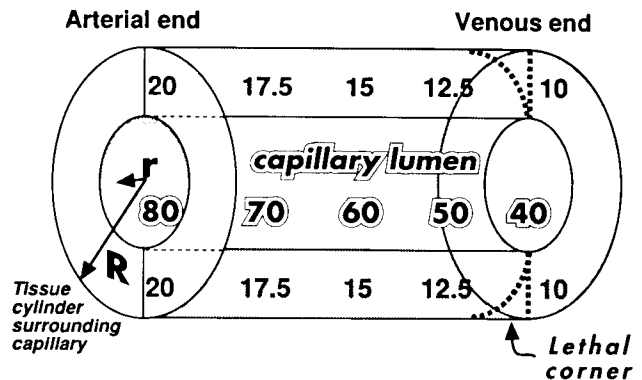
In such a scenario, the perfusionist leaves the ICU asking, "Why?" Why, in spite of providing the patient with blood flow, oxygenation, blood pressure and electrolytes within accepted normal ranges (9), did the patient deteriorate and die? The question can only be answered by understanding that perfusion is the means to achieve a very delicate balance at the cellular level. If the balance can be attained the patient will live. Otherwise, the patient will die. This article is an attempt to explore that critical balance in hopes that with understanding comes insight.

## OXYGEN PRESSURE FIELD THEORY

Oxygen pressure field theory has its origins in two papers published in 1919 by August Krogh (11,12). He explained a model, now called the Krogh cylinder, which describes how oxygen is transported from the capillary lumen to the cells surrounding a capillary. Dr. Krogh developed a mathematical model for predicting oxygen concentration anywhere within this cylinder. There are many variables to consider, such as rate of oxygen consumption, depth of the tissue from the capillary, and arterial and venous  $pO_2$  values. But, the basic concepts of oxygen pressure field theory (13,14) can be explained in a few simple steps while examining the model of the Krogh cylinder in Figure 1. The numbers used in Figure 1 are examples only, and not absolute values. The Fig. 1 cylinder is composed of a capillary with a radius of 5 microns surrounded by a layer of tissue which is 5 microns thick. Using the formula,  $area = \pi r^2$ , the cross sectional area of the capillary is calculated to be 78.5 square microns. The cross sectional area of the entire cylinder is 314 square microns. This means that the cross sectional area of the entire cylinder is exactly four times greater than the cross sectional area of the capillary alone. The next step is to examine the oxygen values brought into the capillary by the blood. In this

**Figure 1**  
**Krogh Tissue Cylinder: Basic Principle**

In the Krogh cylinder, oxygen transfer from the capillary to the tissues is, in part, dependent upon the depth of the tissue surrounding the capillary, the  $pO_2$  of the intracapillary blood, and the driving gradient established between the intracapillary blood and the tissue  $pO_2$ . Oxygen will move into the tissues at the arterial end of the cylinder at a faster rate and at a higher concentration than at the venous end of the cylinder. The result is a wide range of tissue  $pO_2$  values, with the cells at the venous end of the cylinder and furthest away from the capillary being at greatest risk should an imbalance in oxygen delivery or waste product removal occur. (mmHg = millimeters of mercury;  $pO_2$  = partial pressure of oxygen;  $r$  = capillary radius;  $R$  = total cylinder radius;  $u$  = micron; X-section = cross section)

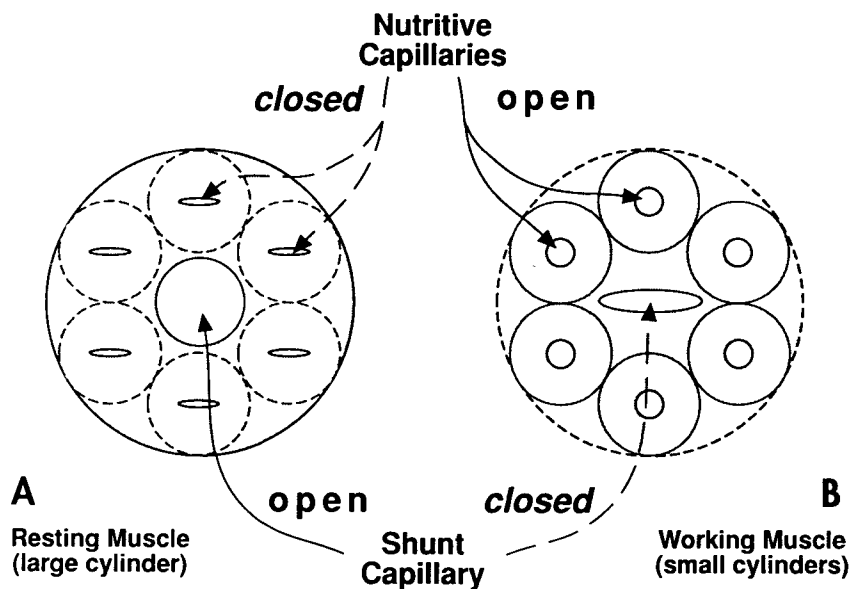


Capillary radius  $r = 5 \mu m$   
 Capillary X-section  $A = \pi r^2 = 78 \mu^2$   
 Cylinder radius  $R = 10 \mu m$   
 Cylinder X-section  $A = \pi R^2 = 314 \mu^2$   
 Ratio :  $\frac{\text{capillary X-section}}{\text{cylinder X-section}} = \frac{1}{4}$

Arterial End:	Venous End:
Capillary $pO_2 = 80 \text{ mmHg}$	Capillary $pO_2 = 40 \text{ mmHg}$
Mean cylinder $pO_2 = 20 \text{ mmHg}$	Mean cylinder $pO_2 = 10 \text{ mmHg}$

**LETHAL CORNER** - area of cylinder at venous end and furthest away from the capillary. Receives the least amount of oxygen and experiences slowest removal of waste products.

case, the blood enters the capillary with an arterial partial pressure ( $paO_2$ ) of 80 millimeters of mercury (mmHg), and leaves the capillary with a venous partial pressure ( $pvO_2$ ) of 40 mmHg. At the arterial end of the capillary, oxygen will diffuse out of the capillary and into a cylinder space four times larger than the capillary cross sectional area alone. Based upon the gas laws, it could be expected that the  $paO_2$  concentration will drop in an inversely proportional manner as the volume of space increases. In this case, the average tissue partial pressure of oxygen ( $ptO_2$ )



**Figure 2**  
**Cross Section: Resting Muscle vs. Working Muscle**

Figure 2A represents the cross section of a tissue cylinder in a resting muscle. The oxygen consumption is low as is the production of waste products. Under these conditions the cylinder can be quite deep. But, as the muscle is put to work, oxygen consumption increases and waste production increases. The microvascular redistribution system increases flow through neighboring capillaries resulting in the formation of shallower, more efficient tissue cylinders, as shown in Figure 2B.

will drop to 20 mmHg, or one fourth of the capillary  $pO_2$  at the arterial end. A similar situation occurs progressively throughout the length of the capillary as the intracapillary  $pO_2$  drops, so that near the venous end of the capillary, with a  $pO_2$  of 40 mmHg, the  $ptO_2$  drops to 10 mmHg. A third item to examine is the driving gradient which results from this distribution of oxygen in the Krogh cylinder. If the arterial  $pO_2$  is 80 mmHg and the average  $ptO_2$  is 20 mmHg, then the driving gradient is 60 mmHg at the arterial end. At the venous end of the cylinder, the  $pO_2$  in the capillary is 40 mmHg and the  $ptO_2$  is 10 mmHg. The driving gradient here is only 30 mmHg. This means that oxygen will move into the tissues faster and deeper at the arterial end of the cylinder than at the venous end.

## THE LETHAL CORNER

By examining the cylinder, it can be seen that the cells which are nearest the arterial end and closest to the capillary wall will receive the most oxygen. Cells which are furthest from the capillary wall at the venous end of the cylinder will receive the least oxygen. The area at the venous end of the cylinder and furthest away from the capillary is called the "lethal corner" (15).

The lethal corner contains cells which receive the least oxygen and contain the highest concentration of waste products. Arterial blood which is low in waste products enters the capillary and begins accumulating waste products from the shallower, closer cells in the tissue cylinder. By the time the blood reaches the venous end, it is carrying a high load of waste products. This reduces the diffusion gradient between venous blood and those cells in the lethal corner. As a result, cells in the lethal corner accumulate higher concentrations of waste products. If an imbalance should occur which would reduce oxygen delivery or

increase the retention of intracellular wastes, the cells in the lethal corner are at the greatest risk.

## MICROVASCULAR REDISTRIBUTION

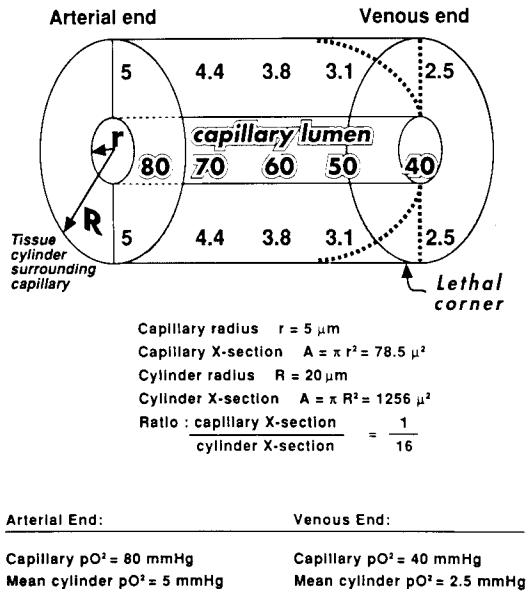
The body has a system called the microvascular redistribution system which minimizes the danger to the cells in the lethal corner (15). Complex interactions of the autonomic nervous system, hormonal system and chemical sensing system all work to readjust blood flow through capillaries when it is needed. See Figure 2.

Anything which causes an imbalance in the microvascular redistribution system can cause a change in the size of the tissue cylinder and, possibly, a change in the size of the lethal corner. For example, a patient on bypass becomes hypertensive and, as a result, nitroprusside is started. This means that with vasodilation caused by the drug, blood may channel through the capillaries of least resistance. This can result in arteriovenous shunting (16,17) through short capillaries and away from the longer "nutritive" capillaries (18,19). Or, steal syndrome (20,21) can result wherein blood is diverted away from capillary beds fed by narrowed or diseased vessels. In either situation, the tissue cylinders in these areas will take on a deeper configuration. Oxygen will have a more difficult time diffusing to the deeper layers of the cylinder and waste products will have a more difficult time diffusing out. This can occur without a noticeable change in the  $pO_2$ . See Figure 3.

The one sign the perfusionist has that the lethal corner has grown is the beginning of an insidious base deficit. The perfusionist can treat the metabolic acidosis with bicarbonate, but this will only correct the pH of the circulating blood. It will do nothing to improve the reduced oxygen delivery to the lethal corner cells

**Figure 3**  
**Krogh Tissue Cylinder: Abnormally Deep**

In this tissue cylinder, the depth has changed for an abnormal reason, but tissue oxygen requirements have not changed. Suppose the depth has doubled over the tissue cylinder depth in Figure 1. At a tissue cylinder radius of 20 microns, the cross sectional area of the Krogh cylinder is 1256 square microns. This is 16 times greater than the cross sectional area of the capillary alone. The estimated average tissue pO<sub>2</sub> at the arterial end of the cylinder will be about 5 mmHg (as opposed to 20 mmHg in Figure 1) and 2.5 mmHg at the venous end. Even though the radial driving gradients are higher than normal, 75 mmHg at the arterial end and 37.5 mmHg at the venous end, they have only increased by about 24%. This in no way can make up for an increase in tissue volume of about 500%. Unless oxygen demand in the tissues is reduced, the cells in the lethal corner will become hypoxic, causing anaerobic metabolism and metabolic acidosis. (mmHg = millimeters of mercury; pO<sub>2</sub> = partial pressure of oxygen; r = capillary radius; R = total cylinder radius; u = micron; X-section = cross section)



Arterial End:	Venous End:
Capillary pO <sub>2</sub> = 80 mmHg	Capillary pO <sub>2</sub> = 40 mmHg
Mean cylinder pO <sub>2</sub> = 5 mmHg	Mean cylinder pO <sub>2</sub> = 2.5 mmHg

**LETHAL CORNER** - compared to Figure 1, volume of cells greatly increased.

(22).

In the short bypass run, the lethal corner cells may tolerate a reduced oxygen concentration for a few hours until cardiac function is restored, the drugs stopped or reduced and the microvascular redistribution system is naturally rebalanced (23). In the long run of extracorporeal support for days or weeks, the lethal corner cells will not tolerate the reduced diffusion of oxygen to the deeper parts of the tissue cylinders.

**PERFUSED CAPILLARY DENSITY**

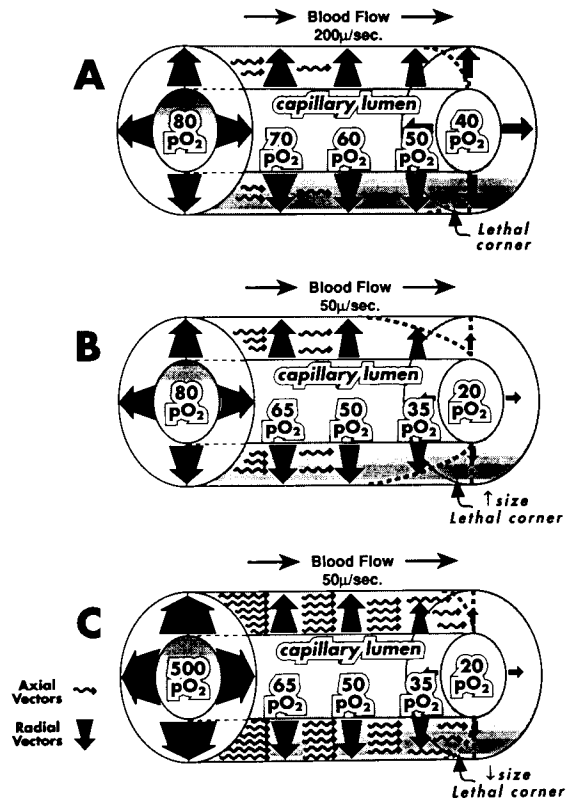
The size of the Krogh cylinder can change as the need for

**Figure 4**  
**Idealized Vectors of Radial and Axial O<sub>2</sub> Diffusion**

Figure 4A represents idealized vectors of radial and axial O<sub>2</sub> diffusion during normal blood flow. The axial pO<sub>2</sub> gradient between the arterial and venous end of the cylinder is: 80 mmHg - 40 mmHg = 40 mmHg. Axial diffusion is minimal.

Figure 4B represents idealized vectors of radial and axial O<sub>2</sub> diffusion during low blood flow conditions. The axial pO<sub>2</sub> gradient between the arterial and venous end of the cylinder is: 80 mmHg - 20 mmHg = 60 mmHg. Axial diffusion is increased but not enough to prevent an increase in the size of the lethal corner.

Figure 4C represents idealized vectors of radial and axial O<sub>2</sub> diffusion during low blood flow conditions and hyperoxia. The axial pO<sub>2</sub> gradient between the arterial and venous end of the cylinder is: 500 mmHg - 20 mmHg = 480 mmHg, an eight-fold increase over Figure 4B. Axial diffusion is greatly augmented because of the increased gradient using hyperoxia (axial kick). This minimizes the size of the lethal corner. (mmHg = millimeters of mercury; pO<sub>2</sub> = partial pressure of oxygen; μ/sec = microns per second)



oxygen changes. This leads to a concept called perfused capillary density (14,24). An organ or tissue at rest will have a relatively small number of capillaries perfused (21). As metabolic demands increase, more capillaries are perfused (25) and the tissue cylinders become smaller and more efficient at distributing oxygen and carrying away waste products. This concept can be seen in the form of capillary refill. Generally, good perfusion causes rapid capillary refill (17,26). This indicates a high density of

perfused capillaries (14). Poor perfusion results in slow capillary refill, or a low density of perfused capillaries. There are exceptions, such as poor skin capillary refill after cardiac surgery (27) and rapid skin capillary refill during high output sepsis (28).

Unfortunately, Dr. Krogh could not go beyond theoretical formulation. But, in the 1970's and 1980's, people such as Kessler (29), Lubbers (13) and Ehrly (30) developed probes which could actually measure intracellular oxygen values. They found that, for the most part, Dr. Krogh was right. The kind of tissue values he predicted were indeed measured in most organs of the body with only minor variations.

The capillary configuration in tissues is completely random. However, this does not result in uniform tissue  $pO_2$  values. Tissue  $pO_2$  values range from the same as the highest  $paO_2$  to as low as zero. The microvascular redistribution system controls capillary blood flow in such a way as to establish an oxygen pressure field within the capillary tissue bed. That oxygen pressure field behaves as if it were a cylinder of tissue around a capillary (13,14,15). The Krogh cylinder, however, does not exist as an anatomical structure. It is a functional structure whose size and shape are defined by  $ptO_2$  measurements and controlled by the microvascular redistribution system according to need.

## APPLYING OXYGEN PRESSURE

### FIELD THEORY

By understanding the things which affect microvascular redistribution and change the cylinder dynamics, the perfusionist can gain new insight on ways to improve long-term perfusion. Examples of these cylinder changes and methods to address them are considered in the following.

The toxicity of hyperoxygenation is very well documented (31). High ventilator  $FiO_2$  values are damaging to lung tissue if used for extended periods. High  $paO_2$  values cause systemic vasoconstriction and capillary maldistribution (32,33,34). Hyperoxia can cause diffusional shunting of oxygen between pre-capillary and post-capillary vessels, resulting in falsely high venous saturations (35,36,37). When used with extracorporeal bypass for the short term, hyperoxia can cause subtle but dangerous problems (38). The lesson here is simple; reduce arterial  $pO_2$  to normal levels, if possible.

The use of normoxia has an important caveat: stagnant hypoxia (24). This occurs when the arterial hemoglobin is fully saturated, but cardiac output is low or, as pertains to the perfusionist, when pump flow is too low. During stagnant hypoxia, the arterial end of the Krogh cylinder is well oxygenated, but the venous end is not. The slow flow of blood through the capillary results in a precipitant drop in intracapillary  $pO_2$ . This is seen as a low mixed venous saturation. See Figure 4.

The normal intracapillary velocity of blood is at least 200 microns per second (39). At this flow, most of the oxygen entering the tissues of the Krogh cylinder comes from radial diffusion from the capillary lumen. Radial diffusion is the move-

ment of oxygen along vectors which are at right angles to the capillary axis. The driving force here is the gradient between the intracapillary  $pO_2$  and the tissue  $pO_2$ .

During stagnant hypoxia, however, the intracapillary  $pO_2$  quickly drops below normal limits (39). The low intracapillary  $pO_2$  at the venous end of the Krogh cylinder results in a very low radial driving gradient. The net result is an increase in the size of the lethal corner.

As the radial gradient in the venous end of the cylinder drops, the gradient between the tissues in the arterial end and the venous end of the cylinder increases (24). As a result, oxygen begins to diffuse from the arterial-end tissues to the venous-end tissues. This diffusion follows vectors which are outside the capillary lumen, but parallel to it. This is called axial diffusion because the vectors parallel the capillary lumen axis (39).

During normal intracapillary blood flow velocity of 200 microns per second or greater, axial diffusion is inconsequential. However, as intracapillary velocity drops, the effect of axial diffusion becomes greater. It has been calculated that as intracapillary velocity drops to 50 microns per second, then 80% of the oxygen entering the venous-end tissues does so by axial diffusion, with only 20% by radial diffusion (39).

Stagnant hypoxia would impair the microvascular redistribution system by reducing the number of perfused capillaries. But, in those capillaries which do receive blood flow, hyperoxia, theoretically, would result in a supersaturation of the arterial-end tissues. This in turn would increase axial diffusion and push more oxygen to the venous-end tissues shrinking the lethal corner. The augmenting of the axial gradient by using hyperoxia during stagnant hypoxia can be called "axial kick", for want of a better term.

Traditionally, it has been taught that increasing arterial  $pO_2$  above 100 mmHg does not significantly increase oxygen content in the arterial blood (40) and therefore does not significantly improve oxygenation. While this is true as long as capillary blood flow velocity is high (37), hyperoxia may be of benefit temporarily by providing axial kick during periods of low capillary blood flow velocity (41). The axial kick improves axial diffusion within the Krogh cylinder, helping to minimize the size of the lethal corner.

However, axial kick is not a long-term substitute for normal blood flow and radial diffusion of  $O_2$ . Even if oxygen reaches the cells of the lethal corner by axial diffusion, the low capillary blood flow will impair the removal of wastes, such as carbon dioxide, from these cells (42). Eventually, the accumulation of wastes will change intracellular pH and damage or kill the lethal corner cells. If the patient does not quickly improve, the perfusionist must find a way to increase intracapillary velocity and improve perfused capillary density or the patient will die.

Imbalances in  $CO_2$  also cause maldistribution in the microvascular redistribution system. While hyperoxia increases  $ptO_2$  mainly near the arterial end of the capillary, hypercapnea raises  $ptO_2$  in all areas (43). This suggests that not only is reducing excessive  $paO_2$  beneficial in the long-term support patient, but

maintaining normal  $\text{paCO}_2$  values in the patient with an increasing base deficit may also be beneficial. Therefore, the use of hypocapnea to compensate for metabolic acidosis may not be the proper maneuver to avoid tissue hypoxia with resulting lactic acid production in long-term support.

Information from Schumacker and Samsel (24) gives the perfusionist another possible tool. They suggest that if intercapillary distance is 40-60 microns (cylinder depth of 20-30 microns), then altered  $p_{50}$  values have little effect on the distribution of oxygen within the cylinder. The  $p_{50}$  is the  $\text{pO}_2$  value at which 50% of the hemoglobin is saturated with oxygen and indicates the position of the oxygen dissociation curve. However, if the intercapillary distance increases (the perfused capillary density drops) then subtle changes in the  $p_{50}$  can have a great effect on oxygen distribution within the cylinders (44). So, if the perfusionist suspects a drop in perfused capillary density because of an increasing base deficit or increasing anion gap, he can improve the radial driving gradient of oxygen within the cylinder by raising the  $p_{50}$ . One option is to increase the arterial  $\text{pCO}_2$  level. Another option would be to add 2,3 diphosphoglycerate to the system by giving fresh red blood cells (45).

If perfused capillary density is low and bicarbonate is given to treat metabolic acidosis, this will shift the  $p_{50}$  the wrong way, reducing the radial gradient and further aggravating the acidosis in the lethal corner cells (22). Of course, one of the waste products of metabolism is  $\text{CO}_2$ . Bicarbonate which is administered migrates to the acidotic tissues and produces large amounts of  $\text{CO}_2$  (46). Because of the structure of the Krogh cylinders, especially when they are enlarged by reduced perfused capillary density, the  $\text{CO}_2$  produced by the bicarbonate and acid reaction in the tissues outside the vasculature and in the lethal corner is not readily removed by the intracapillary blood flow. Studies of changes in tissue  $\text{pCO}_2$  during periods of reduced perfused capillary density such as cardiopulmonary resuscitation or ventricular fibrillation of the heart (42) showed as much as a ten-fold increase in specific tissue  $\text{pCO}_2$ , as high as 400 mmHg, while the mixed venous  $\text{pCO}_2$  increased as little as 10 mmHg above normal baseline values. Once the intracellular  $\text{pCO}_2$  of cardiac tissue reaches 400 mmHg, the tissue damage apparently is irreversible (42). Since the perfusionist can only remove  $\text{CO}_2$  which is in the blood, he or she must optimize perfused capillary density so that waste product removal is facilitated from the Krogh cylinders by the blood flow. Based on oxygen pressure field theory and the dynamics of the Krogh cylinder, the use of bicarbonate would best be limited to treatment of acute, readily reversible episodes of reduced perfused capillary density and not for correction of blood pH over periods of long-term perfusion lasting days or weeks.

Indeed, the need for bicarbonate over lengthy periods of hours or days in the critically ill patient with type A metabolic acidosis (46), in spite of normal arterial and venous oxygen and carbon dioxide values, probably indicates distributive flow abnormalities in the microvasculature and changes in metabolic requirements (47,48). In such a case, if maximum medical management has failed and the criteria are met (49), the patient

may benefit from extracorporeal support in an attempt to improve perfused capillary density. Or, if on such support, a re-evaluation and change of strategy should be considered.

Tissue edema caused by hemodilution in the operating room is usually short lived and normally doesn't present a problem (50). However, a patient requiring "last ditch" extracorporeal support may have significant extravascular fluid volume on board for various reasons. Generalized edema (51) as well as pulmonary edema (52) are associated with increased need for vasopressor and colloid administration as well as morbidity and mortality. One possible explanation is that tissue edema can cause a reduction in  $\text{ptO}_2$  (53,54). This is because edema reduces perfused capillary density by increasing intercapillary distance. As the tissue cylinders deepen from edema,  $\text{ptO}_2$  falls. This decreases oxygen diffusion to the lethal corner cells, which may not be evident in blood gases or venous saturations. The only sign might be an increasing base deficit or anion gap.

The perfusionist needs to assess edema in the patient and decide whether to use ultrafiltration (55,56,57,58,59,60). Urine output might be considered adequate at 1 cc/hr/kg (61,62), but if there is not a net loss of fluid or if there is a weight gain then ultrafiltration needs to be used. Ultrafiltration will reduce tissue edema to improve perfused capillary density and mobilize the patient's endogenous fluid to improve venous return to the heart by increasing the oncotic pressure of the blood. Ultrafiltration needs to proceed at a rate fast enough to help with clinical improvement, but slow enough to prevent intravascular hypovolemia. This can be very difficult, particularly in patients with septic shock (63). Ultrafiltration permits the administration of large volumes of maintenance and nutritive solutions which otherwise might cause or contribute to edema. So finding the optimal ultrafiltration rate depends on the individual patient.

In cardiac patients specifically (64,65,66,67,68), besides improving perfused capillary density, ultrafiltration has the potential to reduce filling pressures in both ventricles without reducing cardiac output. It can also reduce mean right atrial pressure, mean pulmonary artery pressure, pulmonary vascular resistance, wedge pressures and increase mean plasma volume. These benefits occur using slow, continuous ultrafiltration without changing heart rate, mean systolic pressure or systemic vascular resistance. The net effect is an improved cardiac output.

Healing requires good tissue oxygenation (69,70,71). An edematous heart or lungs, even with good blood supply may have trouble just functioning, let alone healing, because of low perfused capillary density and resultant low  $\text{ptO}_2$  values.

Ultrafiltration has the potential, however, to remove large amounts of bicarbonate from the patient. So, if bicarbonate levels drop below normal, careful assessment is needed to determine if the reduced bicarbonate level is due to metabolic acidosis or excessive removal by ultrafiltration. If the former, perfused capillary density needs to be improved. If the latter, supplemental bicarbonate needs to be given (72,73). Lactate buffer solutions should be avoided (74).

## FUTURE TOOLS

Very little work has been done in the field of extracorporeal perfusion using intracellular measurements. But, the information obtained from such measurements can be of great value. For example, one study shows that both bubbler and membrane oxygenators disrupt normal tissue  $pO_2$  values (75), although membrane oxygenators are less disruptive. The study also demonstrates that normal tissue  $pO_2$  values are not restored until hours after the discontinuance of bypass.

Landmark studies by Watanabe (76,77), show the effects of hypothermic extracorporeal support on the brain. During hypothermic bypass there is intracellular retention of  $CO_2$  which causes or contributes to a drop in intracellular pH. This  $CO_2$  retention is not manifested by elevated blood  $pCO_2$  values. Even after rewarming, the intracellular carbon dioxide remains elevated and the intracellular pH remains low at the termination of bypass. This also occurs in skeletal muscle which suggests that the effect is global (49). The effect is the worse with pH stat method, but it is also very prominent using alpha stat method, leading Watanabe to recommend adoption of a method for  $CO_2$  removal more rigorous than alpha stat strategy (76).

Watanabe's studies further show that intracellular  $pO_2$  values remain remarkably constant, averaging 20 mmHg. A common sense argument would suggest that as the patient cooled and oxygen utilization lessened the tissue cylinders should "fill up" with unused oxygen, a reflection of ever increasing venous saturation values commonly seen in hypothermic bypass (50). In other words, the tissue  $pO_2$  value should rise as the patient gets cold.

But, an understanding of the dynamics of the Krogh cylinder explains both the  $CO_2$  retention and low, stable  $pO_2$  values. As oxygen demand is reduced by hypothermia, perfused capillary density should decrease. This results in an increase in the size of each tissue cylinder, balancing the oxygen pressure field with the reduced oxygen utilization. But, because the cylinders become very large and take on a very deep configuration, the removal of waste products such as  $CO_2$  is greatly impaired. So,  $CO_2$  accumulates intracellularly, particularly in the lethal corner cells, causing or contributing to a drop in intracellular pH. Theoretically, hypothermic bypass could safely continue until intracellular  $pCO_2$  approaches 400 mmHg, the point at which cellular damage cannot be reversed, based on another study (42).

Perfusion doctrine teaches that hemodilution improves capillary perfusion on bypass (78), especially during hypothermia, by reducing the viscosity of the blood. In theory, if perfused capillary density is improved by hemodilution, the values reported by Watanabe should not occur. In fact, laser doppler flow studies of the microcirculation demonstrate that microcirculatory flow is reduced on bypass (79), even though overall blood flow to the tissues is not changed. This occurs even with hemodilution at very mild hypothermia; 34 degrees centigrade.

Plainly, microvascular maldistribution and associated or-

gan dysfunction occur during bypass (49). If allowed to continue during long-term support, the outcome for the patient may not be favorable. Paradoxically, in some cases, even multiple organ failure can be improved with the application of extracorporeal support (80,81). Unfortunately, equipment which can measure intracellular pH,  $pCO_2$  and  $pO_2$  and tell the perfusionist quickly about changes at the microvascular level is not yet available for the clinical setting (82). The result is that long-term extracorporeal support becomes trial and error in nature. Until clinicians and perfusionists recognize the need to make such measurements (83), the commercial manufacturers will not respond.

## CRITICISM OF THE KROGH CYLINDER

Although this article has portrayed the Krogh cylinder as a truism, in fact, the microvascular redistribution system is more complicated than the structure of the Krogh cylinder can explain. Many other models have been suggested (15). But, if the perfusionist can understand the basic tenets of the Krogh cylinder, then he or she can begin to understand oxygen pressure field theory and its application in extracorporeal perfusion techniques.

The opportunities for research in this area are enormous. Many questions need answers. For example, what effect does the storage of oxygen on myoglobin have on oxygen transport in the tissue cylinders? In the brain, neurons are mixed with glial cells which have only one tenth the oxygen consumption of neurons. How are the cylinders controlled in that kind of arrangement? The lungs contain "slit" capillaries rather than round tubes. How do cylinders work here? How do cylinders work in the skin where control of heat overrides oxygenation needs? How does atherosclerosis or sickle cell disease affect Krogh cylinder dynamics?

## SUMMARY

Understanding of oxygen pressure field theory, the Krogh cylinder, the lethal corner, perfused capillary density, and microvascular redistribution is valuable in attempts at long-term extracorporeal support. The perfusionist must maintain the balance at the cellular level which not only keeps the patient alive, but allows the injured heart or lungs to heal. This is an enormous challenge for our young profession.

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