Beyond Fick: Discussions On Advanced Perfusion Theory

Session 1: Understanding The Oxygen Pressure Field Using The Krogh Cylinder Model

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No Disclosures

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Objectives

1. Review the origins of the Oxygen Pressure Field Theory (OPFT)

2. Describe the Krogh cylinder model of the oxygen pressure field

3. Describe the Krogh cylinder model of the carbon dioxide pressure field

4. Describe the lethal corner

5. Describe radial and axial vectors of vital gas exchange at the capillary level

6. Describe axial kick and oxygen loading

7. Describe the effect of edema on the oxygen pressure field

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Adolf Fick was a German physician who is known for several things including the description of the law of diffusion of gas across a fluid membrane (1855), the invention of the contact lens (1887) and the description of cardiac function, oxygen delivery and consumption known as the Fick Principle (1870). The Fick principle describes oxygen delivery and oxygen extraction. But this only relates to the macrovascular function of perfusion. In reality the factors that determine tissue oxygenation and carbon dioxide removal at the microvascular level are just as relevant in determining the life or death of the patient. Oxygen Pressure Field Theory (OPFT) describes the details of vital gas exchange at the capillary level. So for perfusionists, OPFT may explain why some patients with seemingly normalized cardiac output, hemodynamic pressure, arterial oxygen saturations and venous oxygen saturations may end up in organ failure or expire of an unexpected complication while other patients who seem to struggle with achieving normal cardiovascular parameters can recover miraculously.

The Fick principle is the foundation of goal directed therapy for the critical care of cardiopulmonary patients. The therapeutic goal for a patient with poor heart or lung function is to normalize hemodynamics and oxygen delivery. This is accomplished by the administration of oxygen and fluids using tools like a ventilator, inotropic drugs and even a heart/lung pump in the most severe cases. At times, successful goal directed therapy fails to reverse the increasing morbidity. Even the use of a heart/lung pump to maintain normal hemodynamics and oxygen delivery can fail to reverse multisystem organ failure or prevent other lethal complications such as stroke and hemorrhage. In these instances an understanding of OPFT can sometimes help to explain this treatment failure phenomenon and provide guidance to a more effective critical care strategy.

The theoretical concepts discussed in this seminar will be the oxygen pressure field, the Krogh cylinder, perfused capillary density, radial and axial gas transfer vectors, anoxic and hypercapnic lethal corners, the carbon dioxide pressure field and the fundamental basis of shock and organ failure. Associated clinical applications discussed will include new ways to assess perfusion, alternative interpretations of blood gases and electrolytes, the corrected anion gap, the venoarterial CO_2 gradient, the Viability Index, base deficits on CPB, edema, ultrafiltration, hypothermic circulatory arrest, gaseous emboli, nitrogen off gassing, the use of normoxia/hyperoxia, oxygen toxicity, reperfusion injury, breaking the reperfusion barrier, reviving expired patients using the ECPR pump and case reports.

August Krogh &
Oxygen Pressure Field Theory (OPFT) Origins

   OPFT was first described by August Krogh in 1918. This concept combined with his many other notable achievements in physiology resulted in his being awarded an unshared Noble Prize in Physiology/Medicine in 1920. But, it wasn't until the 1960's that microvascular probes were developed that could actually measure the oxygen pressure field, confirming the values predicted by Krogh half a century earlier .

Marie & August Krogh, 1904
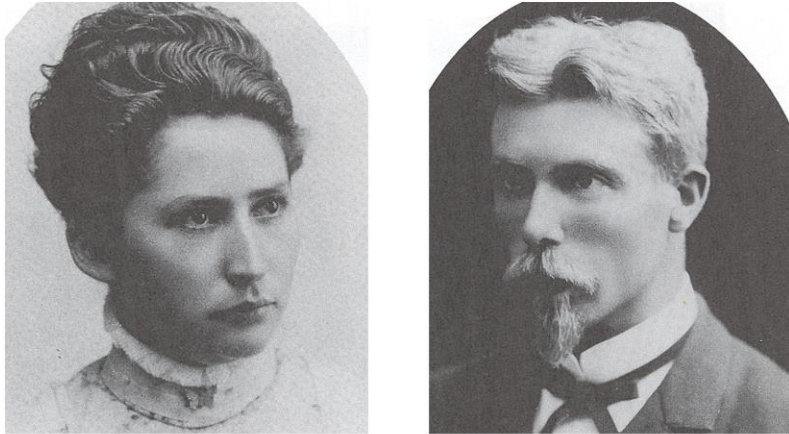
AK, as his loved ones and associates affectionately knew him, was born in Denmark in 1874. He was a brilliant child and by the time he completed his formal education he had taught himself English, French and German in order to read and publish scientific papers in those languages. His contemporaries and associates include Bohr, Haldane, Hasselbalch, Starling, Banting, McLeod and Best. His achievements in science are so numerous that they cannot all be listed here. AK showed that the blood flow in the capillaries has to be regulated through a mechanism that opens and closes the capillaries according to the tissue's need for oxygen. This idea and his scientific proof were at the time so new and revolutionary that he was awarded the Nobel Prize in 1920. His fame in Denmark and all over the world continued to grow until his death in 1949. His scientific discoveries extended from respiration, exercise physiology and capillary physiology into comparative osmoregulation, isotope studies, active transport of ions in plants and animals, and finally insect flight. After insulin's discovery by Banting, Best and McLeod, AK introduced it's production in Denmark in 1922. This saved numerous lives as well as the life of his own wife who had recently developed diabetes. He was the founder of Denmark's Novo-Nordisk, the largest producer of insulin in the world today.

Krogh's wife, Marie, became a physician and a renowned scientist in her own right. Throughout their harmonious marriage and partnership, Marie played an important role in her husband's life both scientifically and personally.

Here are a few of AK's other accomplishments:

1904 – Was the first to predict global warming based on changes in CO_2 in seawater and coal usage in industrialized nations.

1908 – Developed reliable methods and instrumentation for measuring gas tension, particularly O_2 and CO_2, in fluids.

1910 – Proved that gas exchange in the lungs occurred by diffusion. Until this time the scientific consensus was that gases exchanged primarily by excretion and secretion.

Discovering The Respiratory Quotient & Global Warming
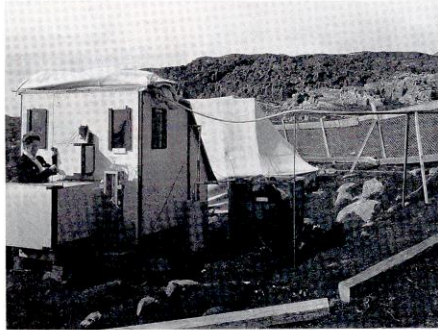
MK next to the respiration chamber in Greenland, July 1908.

The Eskimo hut and its ergometer.

1913 – Made the connection between diet and the type of metabolic function of cells by studying the respiratory patterns of Eskimos. Developed the exercise bicycle (ergometer) to study the connection between muscular work, oxygen consumption and diet. This was the beginning of exercise physiology.

1914 – Discovered the relationship between temperature and metabolic rate and documented the composition of alveolar gas.

1919 – Using a device he called the spectrocomparator, he determined the per cent of saturation of blood hemoglobin with O2 and CO2. "THE SPECTROCOMPARATOR, AN APPARATUS DESIGNED FOR THE DETERMINATION OF THE PERCENTAGE SATURATION OF BLOOD WITH OXYGEN OR CARBON MONOXIDE. BY AUGUST KROGH. The Journal of Physiology, Volume 52, Issue 5, 25 MAR 1919 (From the Laboratory of Zoophysiology, Copenhagen University.)" This year he also published his work on the structure and function of capillaries (part of which would later become known as the Oxygen Pressure Field Theory) for which he won an unshared Noble prize in 1920.

1920 – He discovered the relative value of fat and carbohydrates as sources of muscular energy, thus describing the respiratory quotient.

1923 – At the request of Banting, MacLeod and Best, Krogh was the first to develop a practical way to mass-produce insulin. This not only provided an invaluable service to mankind, but also at the same time saved the life of his own wife, Marie Krogh, who developed diabetes just a few years earlier. Marie Krogh was a medical doctor and a famous scientist in her own right. Based on work done by AK, Marie developed minimal nutrition standards for children and was instrumental in getting government support to promote these standards in the Danish schools. This idea is applied in all industrialized countries today. In the USA it is overseen as the USDA Minimum Dietary Requirements. She is also credited with developing 'biological standardization' which was first used to standardize dosages for medications such as digitalis; changing it from a deadly poison to the most useful of cardiac medications.

Blood Gas Analysis & The Iron Lung
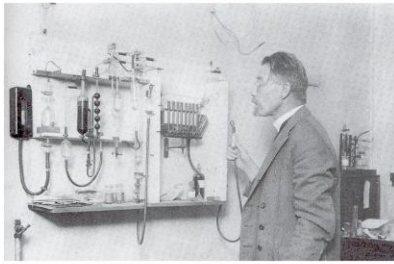
Cecil Drinker & AK

1931 – He developed the syringe pipette. This may not seem like a very important thing compared to wining a Nobel Prize, but until this time the accurate and repeatable measurement of fluids within a laboratory and between laboratories trying to replicate experiments was almost impossible.

1932 – Based on the ideas of Cecil and Phillip Drinker of the Harvard Medical School and at their request, AK built the first practical ventilator to treat polio victims. Today we call this machine the "iron lung". He was also the first to measure and document the importance of venous pressure and colloid oncotic pressure.

1936 – Described and measured insensible fluid loss.

1939 – Discovered the "ion pump" in cells.

1946 – Discovered living membrane potentials and described 'active transport' for the first time.

Studying How Insects Fly!
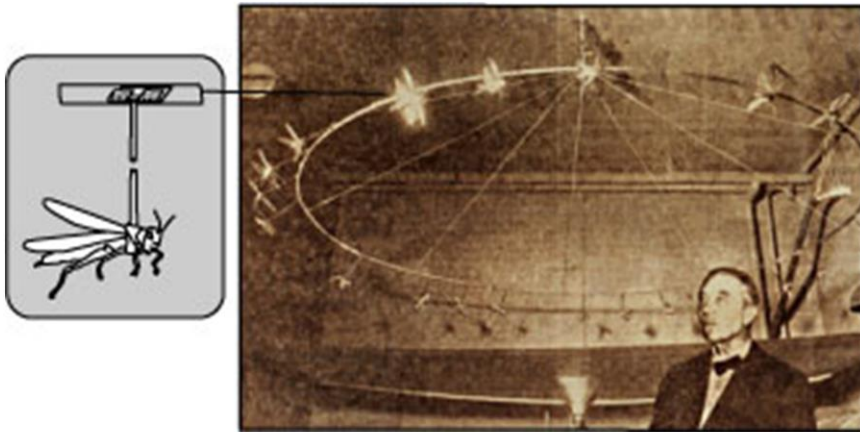
These things are by no means the limit of his work. During his career he was the first to use an incubator for premature infants. He improved on the understanding of the Fick principle by developing methods of measuring cardiac output using nitrous oxide and carbon monoxide in respiratory gases. His instruments for measuring gases in fluids made the measurement of blood gases possible. He developed a means to identify specific types of lab animals that were best suited for various experiments. He was one of the first scientists to use statistical analysis and he was one of the first to promote the need for reproducibility of experiments. He wrote scientific papers covering a wide range of subjects, including:

On the composition of the air in the tracheal system of some insects.
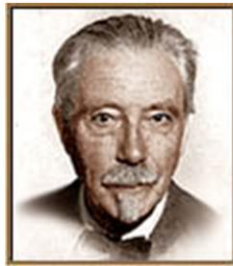
Ethyl urethane as a narcotic for aquatic animals.

Physiology of the blue whale.

The dust problem in museums and how to solve it.

A roundabout for studying sustained flight of locusts.

Institutes, Insulin, Stamps, Pictures & Portraits

   Despite all of these accomplishments, August Krogh was the most humble and non-obtrusive of men. In fact, he attracted so little attention to himself that on October 28, 1920 when reporters approached the administration of the University of Copenhagen and asked for Dr. August Krogh who had just won an unshared Nobel Prize for physiology/medicine they were told, "It must be a mistake, there is no Danish professor with that name." However the legacy left by August Krogh is so great that it is still having an impact on physiology and medical science today. It will soon have an impact on the future of the perfusion profession because his concepts of capillary function and oxygen distribution are just as valid today as they were 94 years ago when he won the Noble Prize for them. His concept of the oxygen pressure field holds answers to many questions to which perfusionists must find answers. Only now, with our pumps and oxygenators, can perfusionists begin manipulate the oxygen pressure field. In controlling the oxygen pressure field perfusionists have the potential to reverse shock and multiple organ failure and treat such deadly conditions as adult respiratory distress syndrome or sepsis. These two conditions alone account for hundreds of thousands of hospital deaths every year.
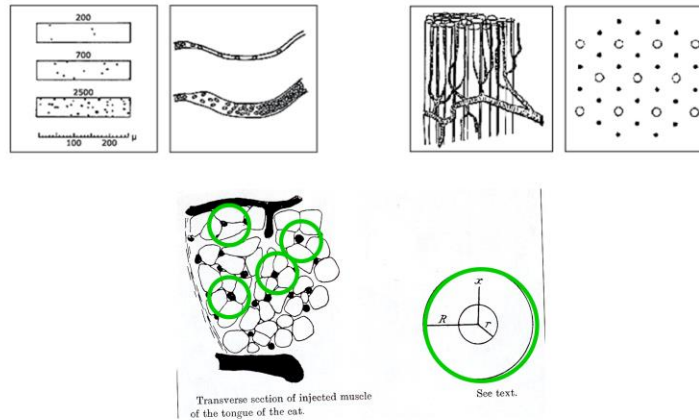
Drawings from August Krogh's work on capillaries that illustrates the concept of perfused capillary density, the Krogh cylinder and the oxygen pressure field.

Krogh realized that capillaries spontaneously opened and closed as the need for oxygen increased or decreased. The pattern of opening and closing was not random, but occurred so that the open capillaries remained equidistant no matter how many were open. He realized that biological systems conserved energy by minimizing perfusion during times of low physiologic demand and maximizing it during periods of high demand. From this concept he was able to derive a math formula to describe how oxygen is distributed throughout the tissues during low and high demands.
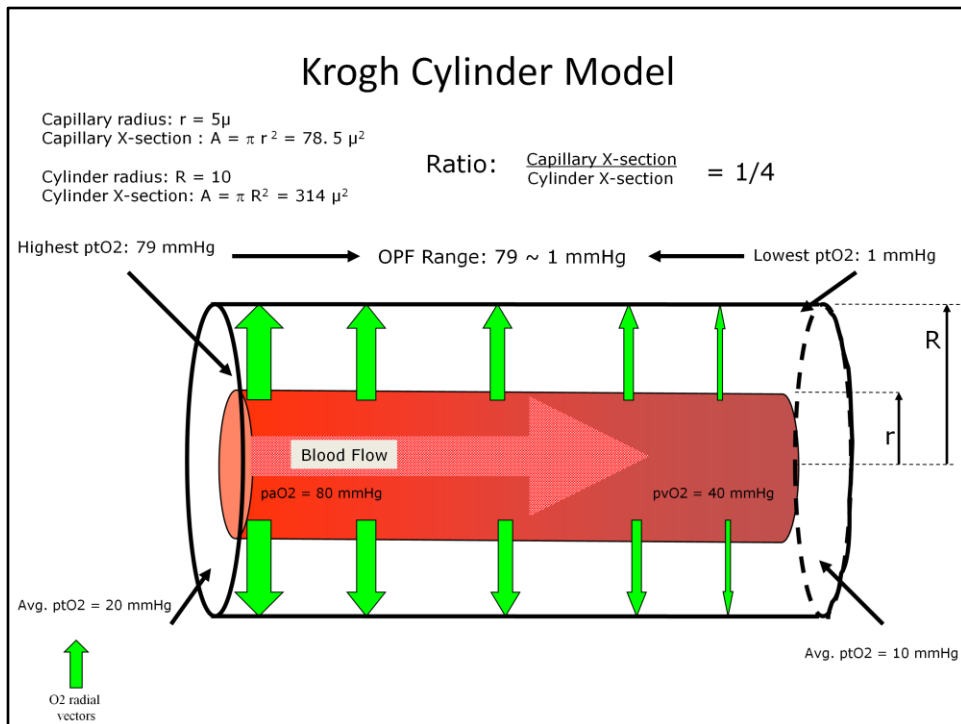
Diagram example of the fundamental concept of the Krogh cylinder and the oxygen pressure field values.

The Krogh cylinder model is a simple way to describe an oxygen pressure field. Dr. Krogh envisioned a capillary surrounded by a sleeve of tissue to which the capillary provided gas exchange and nutrients. The tissue cylinder pictured here as an example has a capillary radius of 5 microns (μ) and a cylinder radius of 10 μ. This results in a capillary-to-cylinder cross-sectional area and volume relationship of 1:4. As blood enters the capillary the oxygen leaves the hemoglobin to expand out of the capillary and into the cylinder volume made up of the living tissues. In this example, the arterial pO2 value of the blood entering the capillary remains steady at 80 mmHg. The oxygen will expand into the arterial-end tissues of the cylinder resulting in a stable average tissue pO2 of 20 mmHg. At the venous end of the cylinder the intracapillary pO2 of the blood has fallen to 40 mmHg and after expanding into the cylinder volume the average tissue pO2 will be 10 mmHg.

At the arterial end of the cylinder and near the capillary itself the tissue pO2 may be almost equal to the arterial pO2 of the blood (79 mmHg). At the venous end of the cylinder and farthest from the capillary the tissue pO2 may approach zero (1 mmHg). The oxygen pressure field in the tissues around this capillary has a range of 79 mmHg to 1 mmHg. The median value would be approximately 20 mmHg, meaning that 50% of the tissues have pO2 values greater than 20 mmHg and 50% have values less than 20 mmHg.

The oxygen unloads from the capillary blood and follows radial vectors to enter the tissue. Radial vectors move at right angles to the capillary axis. The strength of the vectors (gradient) depends upon the intracapillary pO2 value and the tissue pO2 value. At the arterial end the capillary pO2 is 80 mmHg and the tissue pO2 is 20 mmHg; the gradient would be 60 mmHg. At the venous end the capillary pO2 is 40 mmHg and the tissue pO2 is 10 mmHg; the gradient would be only 30 mmHg. This means that more O2 will move into the cylinder at a faster rate at the arterial end than at the venous end of the cylinder. The values shown here are not absolute but serve only as examples.

Cylinder Model Capillary Video

Courtesy of Dr. Christopher Ellis PhD, Professor and Graduate Chair, Department of Medical Biophysics, Faculty of Medicine, University of Western Ontario, London, Ontario

3D Field of View arteriolar layer

z=92 um

This video is a good example of why Dr. Krogh chose the cylinder configuration for his model. The camera focuses from a depth of 92 μ to 18 μ through a living rat skeletal muscle. As the picture moves deep to shallow, open capillaries appear in parallel configuration following the muscle fiber orientation. The distance between adjacent capillaries can be measured and used to calculate the radius of the tissue sleeve around each capillary. These radii can then be averaged to calculate the size of the average Krogh cylinder.

In resting muscle the number of open capillaries is relatively small because the need for oxygen delivery and carbon dioxide removal is relatively small. However if the muscle were to begin working the number of open capillaries would increase. This would make each Krogh cylinder smaller and shallower, resulting in much more efficient oxygen delivery and carbon dioxide removal to meet the increased metabolic need. Because this is a resting muscle, this capillary recruitment phenomenon is not seen in this video. However the viewer can see several shunt capillaries that quickly open and close spontaneously in order to balance minor metabolic imbalances within the tissue.

The number of open capillaries within a specific volume of tissue is called perfused capillary density (PCD). PCD normally changes as the metabolic need changes, increasing as metabolic need increases and decreasing as metabolic need decreases.

Video is by courtesy of Dr. Christopher Ellis PhD, Professor and Graduate Chair, Department of Medical Biophysics, Faculty of Medicine, University of Western Ontario, London, Ontario.
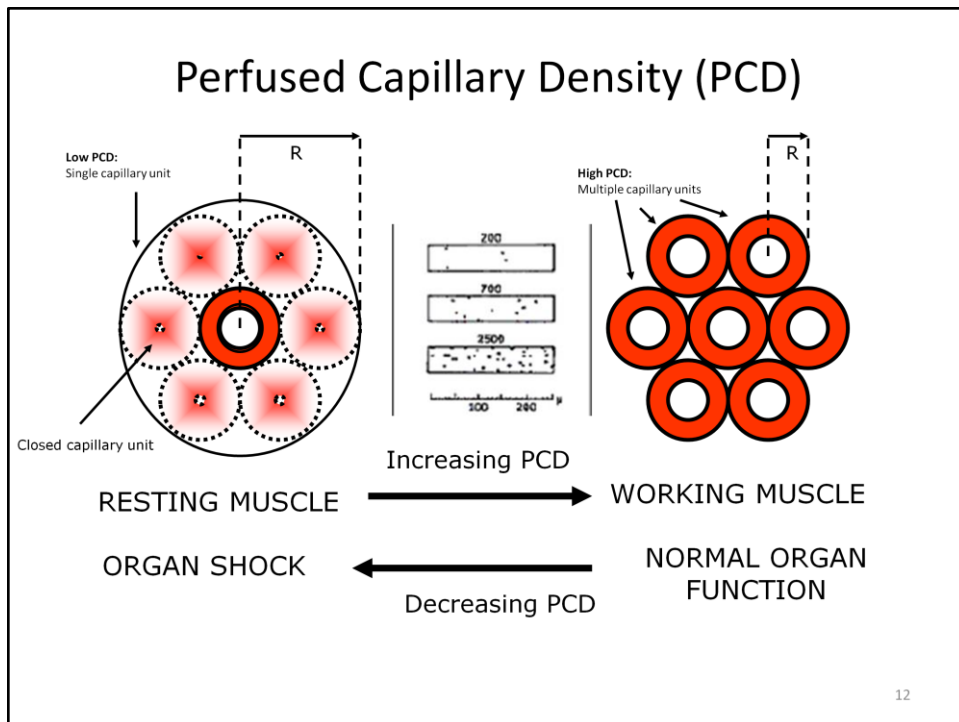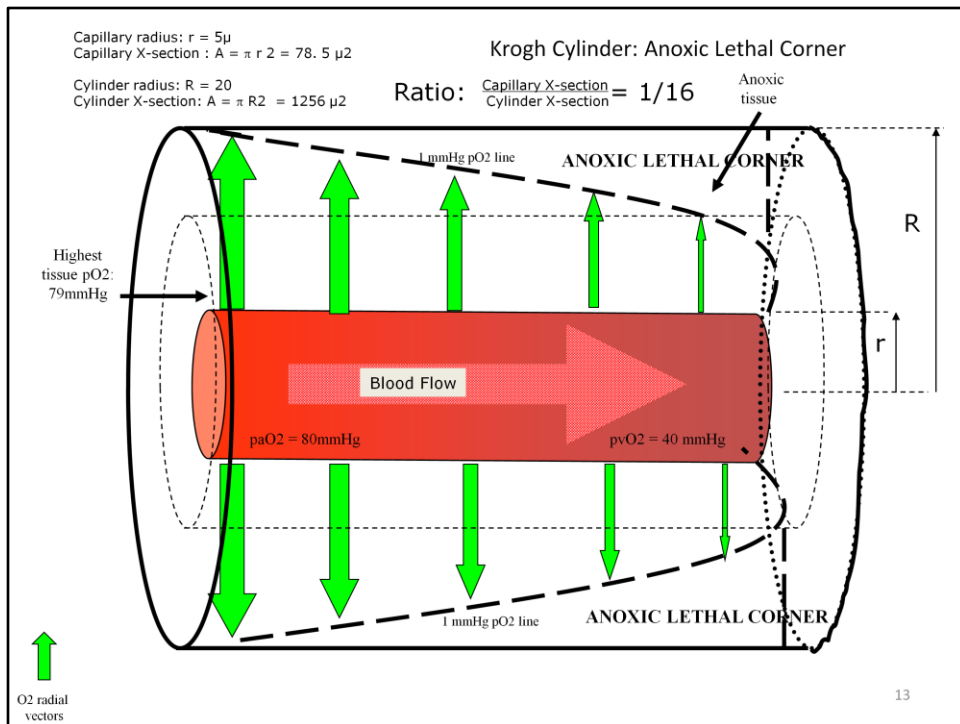
Perfused Capillary Density (PCD)

Perfused capillary density changes as the metabolic demands change. Failure to increase PCD during times of stress is pathologic and may be associated with the health state of the patient.

   In resting tissues the number of open capillaries is relatively small because the need for oxygen delivery and carbon dioxide removal is relatively small. However if the tissues begin working or consuming greater amounts of oxygen, the number of open capillaries normally increases. As additional capillaries open, smaller and shallower Krogh cylinders form resulting in much more efficient oxygen delivery and carbon dioxide removal to meet the increased metabolic need. The number of open capillaries within a specific volume of tissue is called perfused capillary density (PCD). PCD normally changes as the metabolic need changes, increasing as metabolic need increases and decreasing as metabolic need decreases, such as when muscles start or stop working.
   The body's ability to open and close capillaries is the key to maintaining homeostasis in any type of tissue without excessive utilization of physiologic resources. When the need for oxygen is diminished there are fewer open capillaries and the Krogh cylinder is relatively large and deep. When oxygen need is increased cardiac output increases and more capillaries open. The Krogh cylinder becomes smaller and shallower and more efficient at distributing oxygen to the mitochondria. However during illness additional needed capillaries may fail to open and some open capillaries may close, resulting in a decrease in PCD. This phenomenon has many etiologies such as cardiac failure, blood loss, infection, spinal nerve damage, etc. However, they are all grouped under a common diagnosis called "shock".
   Shock occurs when the body fails to open an adequate number of capillaries to supply oxygen and remove carbon dioxide; i.e., PCD is inadequate to support life. So in OPFT terms, shock is simply inadequate PCD. Frequently shock is defined as inadequate cardiac output or inadequate oxygen delivery. However shock can occur even if cardiac output and oxygenation seem normal. This is because PCD in vital organs cannot be quantified clinically using the customary assessments. When poor PCD occurs the condition is termed a 'lethal corner'.

Krogh Cylinder: Anoxic Lethal Corner

Capillary radius: r = 5μ
Capillary X-section : A = π r 2 = 78. 5 μ2

Cylinder radius: R = 20
Cylinder X-section: A = π R2 = 1256 μ2

Ratio: $\frac{\text{Capillary X-section}}{\text{Cylinder X-section}}$ = 1/16

Anoxic tissue

1 mmHg pO2 line   ANOXIC LETHAL CORNER

R

Highest tissue pO2: 79mmHg

r

Blood Flow

paO2 = 80mmHg   pvO2 = 40 mmHg

1 mmHg pO2 line   ANOXIC LETHAL CORNER

O2 radial vectors

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Reductions in PCD can result in exponentially large increases in the Krogh cylinder configuration leading to the development of a lethal corner.

During a disease state, cardiac output may not be able to increase or even maintain the volume necessary to preserve adequate homeostasis. PCD becomes less than is required to meet the demands of the tissues. So the Krogh cylinder becomes too large and too deep to allow for the adequate distribution of oxygen to the needy mitochondria and removal of acidifying carbon dioxide. Reduced PCD changes the relationship between the capillary cross-section and the cylinder cross-section. The Krogh cylinder seen here develops as a result of a pathologic or iatrogenic reduction in PCD. The capillary radius is still 5 μ, but the cylinder radius has increased from 10μ as seen in the previous model to 20 μ , making the capillary-to-cylinder cross-sectional ratio 1:16. This cylinder is too large for the radial vectors to adequately oxygenate the tissues surrounding the distal capillary. This capillary then fails to provide enough oxygen to a tissue volume that is almost 4 times greater than seen in the earlier 1:4 cylinder example. The result is an area of anoxic tissue called the 'lethal corner' near the distal periphery of the cylinder.

The oxygen pressure field within this cylinder has a range of 79 mmHg to 0 mmHg, but the median value is only about 5 mmHg instead of 20 mmHg. So 50% of the tissues have pO2 values greater than 5 mmHg and 50% have values less than 5 mmHg with a large portion receiving no oxygen at all.

Even in a disease state, cardiac output may *seem* adequate, intracapillary blood flow velocity may s*eem* normal and oxygen extraction may also *seem* normal. But radial vectors may be too low in magnitude to adequately fill the distal corners of a large cylinder with oxygen. So an anoxic lethal corner forms. The result is a situation where normoxic, hypoxic and anoxic mitochondria exist simultaneously within the same capillary bed. The size of the lethal corner is determined by the number of anoxic mitochondria present. Organic acid waste products accumulate in the lethal corner as the anoxic mitochondria convert to anaerobic metabolism. The tissue pH decreases impairing enzymatic function in local tissues and, ultimately, organ function as a whole. A common medical term used to describe this situation is "shock".
The formation of an anoxic lethal corner may be an unrecognized but common complication of routine cardiopulmonary bypass. Despite the maintenance of vital perfusion parameters within the normal range a base deficit frequently develops on pump or in the immediate post-pump time period. This probably indicates a detrimental change in PCD during cardiopulmonary bypass.
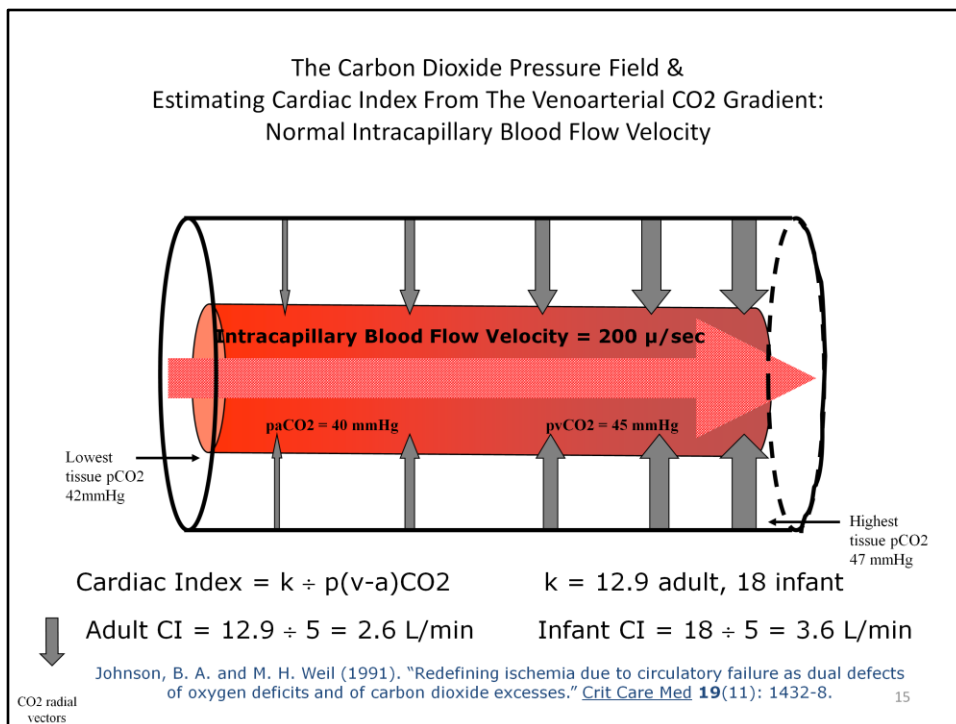
Compartment Model Capillary Video
Jaryszak EM et al. JAP 89(3),1233-38, Sep 2000 With Permission

The Krogh cylinder is a useful model to explain the effect that changes in perfused capillary density have on capillary gas transfer and the development of the lethal corner. However except for muscle tissue, capillary configuration in other tissues is usually completely random and redundant like twigs on a tree branch. This video demonstrates how the concept of a lethal corner can exist outside of the Krogh cylinder model. In the center of the screen is an amorphic tissue mass. Capillary blood flow can be seen moving around the periphery of this mass. The central area of the tissue mass is relatively distant from the capillary blood flow. So oxygen concentration would be lowest and carbon dioxide concentration would be highest in this central area; constituting the lethal corner. If this were a glomerulus in a kidney, the patient would not be making much urine. Or if this were an area of gray matter in the brain, the patient might be stuperous or unconscious. If the situation were allowed to continue, serious complications like kidney failure or brain infarction could occur. However at a certain point when conditions are appropriate, capillaries within the tissue mass spontaneously open (perfused capillary density increases), dividing the mass into much smaller areas, thus eliminating the lethal corner.

This concept is called the compartment model (as opposed to the Krogh cylinder model) because as perfused capillary density changes larger or smaller compartments of tissue are formed. With low perfused capillary density the compartments are big with greater potential for development of a lethal corner. With high perfused capillary density the compartments are smaller with less potential for development of a lethal corner.
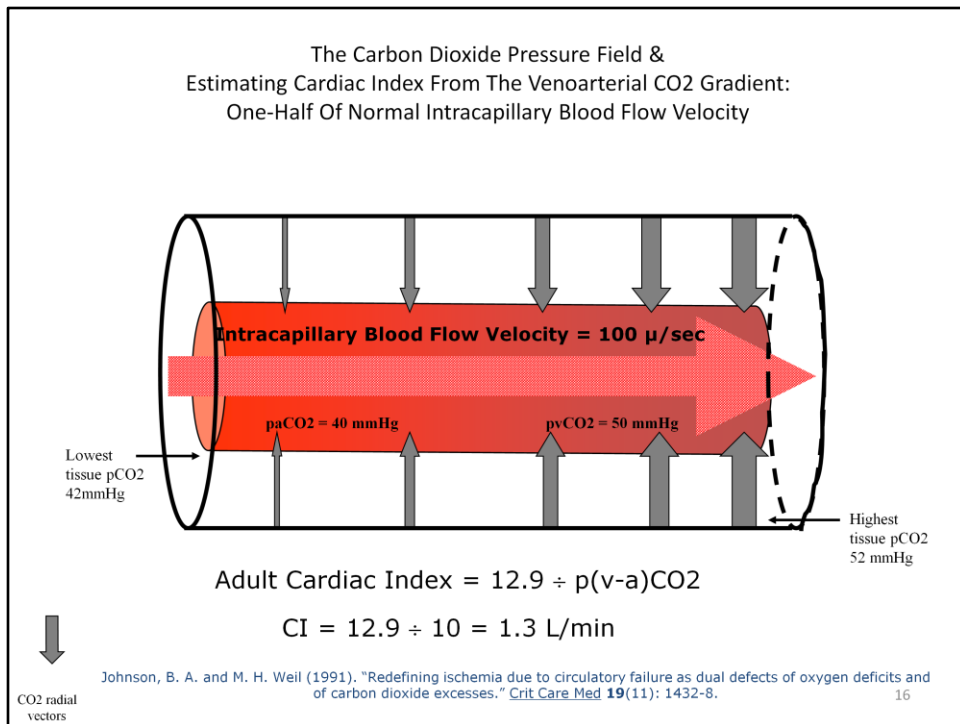
This video is actually of a living lung alveolus. It dramatically illustrates how quickly capillary recruitment can change for the better or for the worse in patients with pulmonary disease. Video courtesy of the Journal of Applied Physiology.

The Carbon Dioxide Pressure Field &
Estimating Cardiac Index From The Venoarterial CO2 Gradient:
Normal Intracapillary Blood Flow Velocity

Intracapillary Blood Flow Velocity = 200 µ/sec

paCO2 = 40 mmHg   pvCO2 = 45 mmHg

Lowest tissue pCO2 42mmHg

Highest tissue pCO2 47 mmHg

Cardiac Index = k ÷ p(v-a)CO2   k = 12.9 adult, 18 infant

Adult CI = 12.9 ÷ 5 = 2.6 L/min   Infant CI = 18 ÷ 5 = 3.6 L/min

Johnson, B. A. and M. H. Weil (1991). "Redefining ischemia due to circulatory failure as dual defects of oxygen deficits and of carbon dioxide excesses." Crit Care Med **19**(11): 1432-8.

CO2 radial vectors

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The carbon dioxide pressure field normally has small gradients due to the high solubility of CO2. The formula for calculating the cardiac index using the venoarterial CO2 gradient comes from Johnson & Weil, 1991.

The formation of an anoxic lethal corner is not the only mechanism that can result in tissue acidosis. The trapping and retention of carbon dioxide in the lethal corner area also occurs and can be described using the Krogh cylinder model. This phenomenon is particularly deadly because it is almost totally unknown to clinicians caring for critically ill cardiopulmonary patients and it can occur without any deviation of the arterial blood gas from normal values or a change in hemodynamic parameters.

There is a carbon dioxide pressure field but it does not normally have the large range of values like those seen in the oxygen pressure field . Carbon dioxide is 23 times more soluble in water than oxygen, so it requires only 1/23rd the gradient needed by oxygen for removal from the Krogh cylinder. Carbon dioxide has its highest concentration in the distal corner of the Krogh cylinder and its lowest concentration at the capillary's proximal end, nearest the capillary wall; the opposite configuration of the oxygen pressure field. In this illustration, the arterial blood pCO2 is 40 mmHg and the arterial-end tissue pCO2 is 42 mmHg. The venous blood pCO2 is 45 mmHg and the venous-end tissue pCO2 is 47 mmHg. As long as the intracapillary velocity of the blood remains normal (~200 µ/sec) and the diameter of the Krogh cylinder does not change, then adequate amounts of carbon dioxide will be removed from the tissues. The evidence of this is a normal venoarterial carbon dioxide gradient (p[v-a]CO2) which is about 5 to 7 mmHg. Since the p[v-a]CO2 is in part dependent on the intracapillary velocity of the blood, the cardiac index can be estimated from the p[v-a]CO2. In adults, dividing the constant "12.9" by the p[v-a]CO2 gives an estimate of the cardiac index with R=0.76 and R^2 = 0.58. In the younger the patient, the constant is larger. This is because of the higher metabolic rate in younger patients. In infants the constant is estimated at 18.
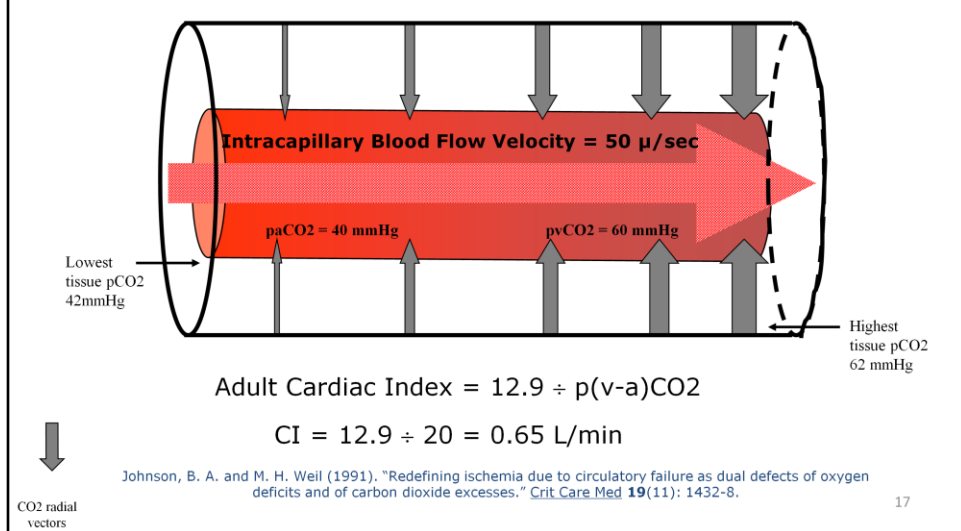
The Carbon Dioxide Pressure Field &
Estimating Cardiac Index From The Venoarterial CO2 Gradient:
One-Half Of Normal Intracapillary Blood Flow Velocity

Reduction in intracapillary blood flow velocity results in an increase in the venoarterial CO2 gradient and an increase in the CO2 concentration in the lethal corner area.

Mathematically if the intracapillary blood flow velocity decreases by 50%, the p[v-a]CO2 will double. In this example, the p[v-a]CO2 is 10 mmHg because intracapillary blood flow velocity has fallen from 200 to only 100μ/sec. This results in an increased carbon dioxide concentration in the tissues, especially the lethal corner area. Correspondingly the intracellular acidosis worsens. Similar to the way that the intracellular pH decreases due to the accumulation of organic acid waste products from anaerobic metabolism, the accumulation of CO2 causes the intracellular milieu to become inhospitable to normal enzymatic function resulting in the eventual impairment of organ function. This can occur even if tissue oxygenation is adequate.
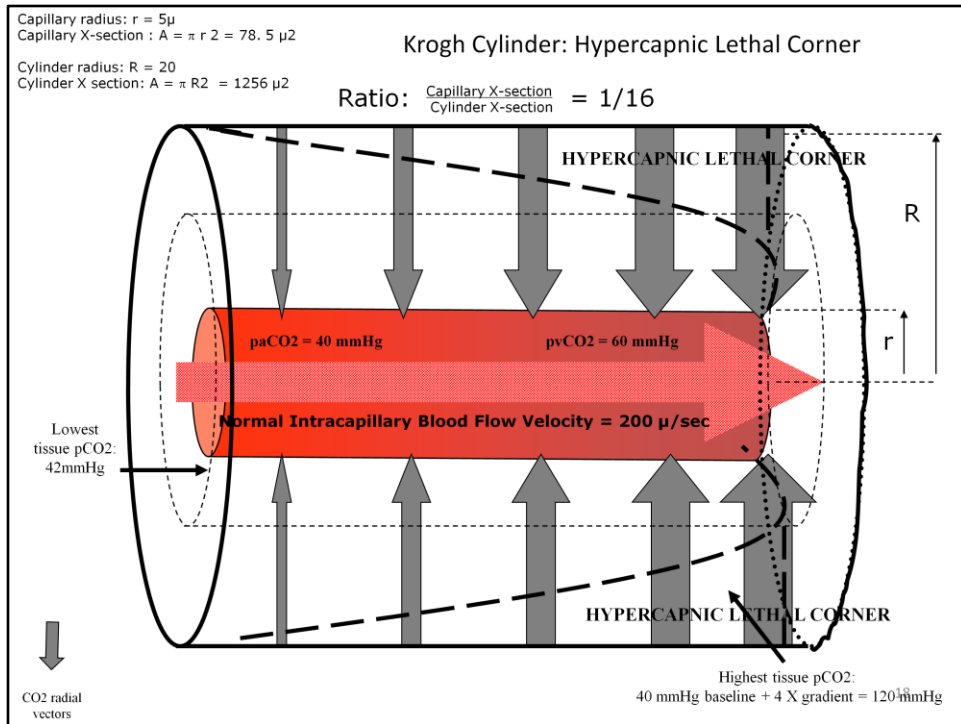
The Carbon Dioxide Pressure Field &
Estimating Cardiac Index From The Venoarterial CO2 Gradient:
One-Fourth Of Normal Intracapillary Blood Flow Velocity

Intracapillary Blood Flow Velocity = 50 μ/sec

paCO2 = 40 mmHg   pvCO2 = 60 mmHg

Lowest tissue pCO2 42mmHg

Highest tissue pCO2 62 mmHg

Adult Cardiac Index = 12.9 ÷ p(v-a)CO2

CI = 12.9 ÷ 20 = 0.65 L/min

Johnson, B. A. and M. H. Weil (1991). "Redefining ischemia due to circulatory failure as dual defects of oxygen deficits and of carbon dioxide excesses." Crit Care Med **19**(11): 1432-8.

CO2 radial vectors

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A reduction in the intracapillary blood flow velocity to only 25% of normal results in a 4 fold increase in the venoarterial CO2 gradient and greater retention of CO2 within the lethal corner area.

If the intracapillary blood flow velocity should drop to 25% of normal, the p[v-a]CO2 would quadruple and even more carbon dioxide will be retained in the lethal corner tissues, further depressing the pH and compromising homeostasis.

Krogh Cylinder: Hypercapnic Lethal Corner

Capillary radius: r = 5μ
Capillary X-section : $A = \pi r^2 = 78.5 \mu^2$

Cylinder radius: R = 20
Cylinder X section: $A = \pi R^2 = 1256 \mu^2$

Ratio: $\frac{Capillary\ X\text{-}section}{Cylinder\ X\text{-}section} = 1/16$

HYPERCAPNIC LETHAL CORNER

R

r

paCO2 = 40 mmHg   pvCO2 = 60 mmHg

Normal Intracapillary Blood Flow Velocity = 200 μ/sec

Lowest tissue pCO2: 42mmHg

HYPERCAPNIC LETHAL CORNER

CO2 radial vectors

Highest tissue pCO2:
40 mmHg baseline + 4 X gradient = 120 mmHg

Pathologic or iatrogenic decreases in PCD can result in exponential increases in CO2 retention within the lethal corner area.
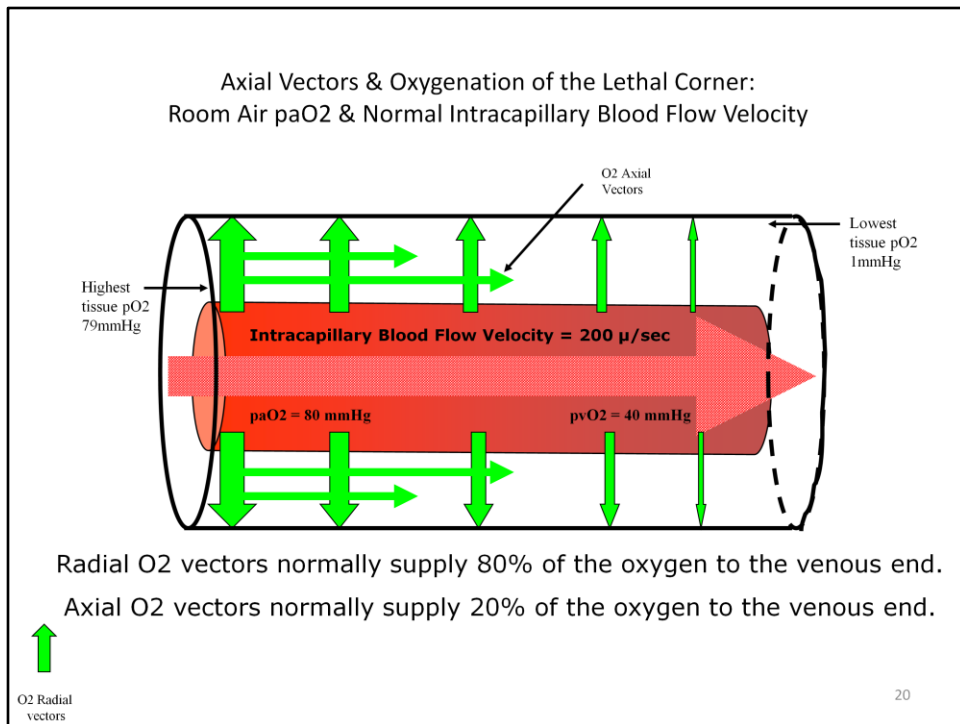
   A decrease in intracapillary blood flow velocity is, theoretically, an important cause of the linear retention of carbon dioxide in the lethal corner. However the result of a decreased cardiac index would more likely result in a reduction of PCD. An exponential increase rather than a linear increase in the retention of carbon dioxide would then occur, resulting in a hypercapnic lethal corner. If PCD decreases and the cylinder radius doubles, the capillary-to-cylinder ratio changes from 1:4 to 1:16. Since the tissue volume around the open capillary has increased by almost a factor of four, this single capillary will need to remove four times more carbon dioxide than it normally would in a 1:4 cylinder. This will overload the capillary's capacity to remove carbon dioxide from the tissues and cause the massive retention of carbon dioxide within the lethal corner. If the patient experiences both a reduction in intracapillary blood flow velocity and a decrease in perfused capillary density the retention of carbon dioxide in the lethal corner can be tremendous. An estimate of the carbon dioxide trapped in the lethal corner tissues can be made by adding the arterial pCO2 to four times the p[v-a]CO2. In this example, the lethal corner carbon dioxide concentration would be about 120 mmHg. Unless this situation is reversed quickly by increasing the blood flow and increasing perfused capillary density, the patient will expire.
   A goal directed therapy that focuses on oxygen delivery may miss the development of a hypercapnic lethal corner because the arterial pCO2, arterial oxygen saturation and even the hemodynamics may be normal. But at some point the patient's organ function will begin to falter due to the hypercapnic lethal corner.
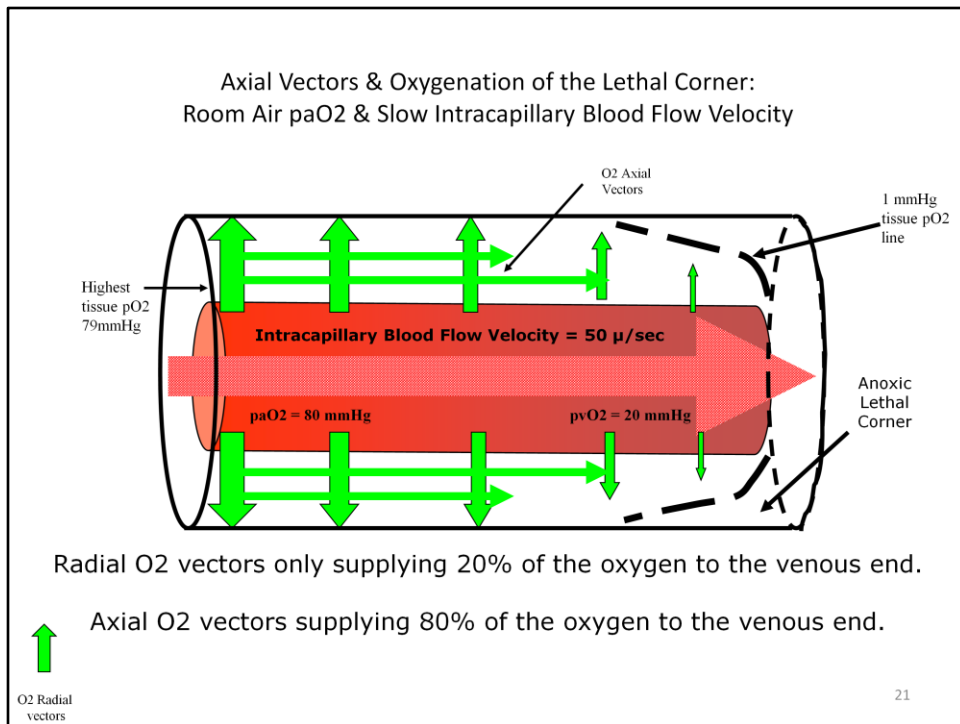
Coincident Lethal Corners
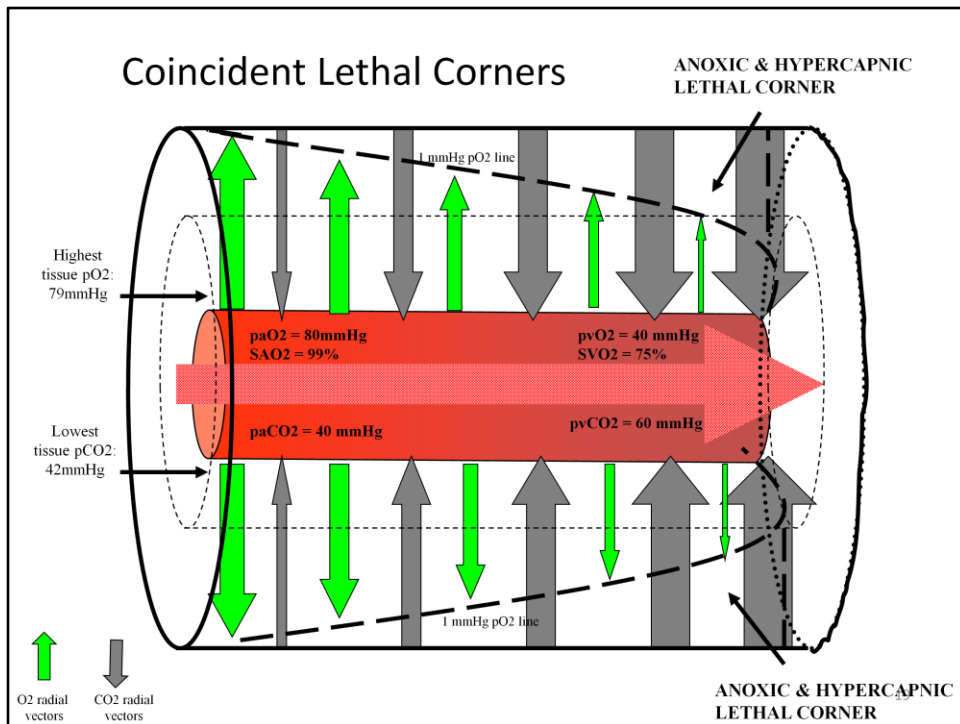
A pathologic or iatrogenic decrease in PCD can result in the development of both an anoxic and hypercapnic lethal corner.

   The Krogh cylinder model has illustrated the potential for two different kinds of lethal corners; anoxic and hypercapnic. This example combines the two concepts within a single 1:16 cylinder model. The development of a lethal corner is most likely the result of a pathologic or iatrogenic decrease in PCD. This example implies that both the anoxic and hypercapnic lethal corners would occur simultaneously. However either the anoxic or the hypercapnic lethal corner can develop independently, as well as simultaneously. A patient with both an anoxic lethal corner and a hypercapnic lethal corner simultaneously is at very high risk of death.

Axial Vectors & Oxygenation of the Lethal Corner:
Room Air paO2 & Normal Intracapillary Blood Flow Velocity

O2 Axial Vectors

Lowest tissue pO2 1mmHg

Highest tissue pO2 79mmHg

Intracapillary Blood Flow Velocity = 200 μ/sec

paO2 = 80 mmHg   pvO2 = 40 mmHg

Radial O2 vectors normally supply 80% of the oxygen to the venous end.

Axial O2 vectors normally supply 20% of the oxygen to the venous end.

O2 Radial vectors

Axial oxygen vectors normally supply about 20% of the oxygen needs of the venous-end tissues.

   Another aspect of OPFT that is important to perfusionists is the presence of axial oxygen vectors and gradients. Radial vectors radiate at right angles from the central axis of the capillary. Axial vectors run parallel to the axis of the capillary within the substance of the tissue sleeve. In a healthy patient most of the oxygen that enters the tissues moves along radial vectors between the blood in the capillary and the tissues. But as discussed earlier, there is more oxygen in the arterial-end tissues of the cylinder than in the venous-end tissues. As a result, oxygen flows from the arterial-end tissues towards the venous-end tissues along vectors outside of but parallel to the axis of the capillary; axial vectors. Normally only 20% of the oxygen entering the venous-end tissues comes from axial vectors while 80% comes from radial vectors. The magnitude of the axial gradient depends on the difference in tissue oxygen concentration between the arterial-end tissues and the venous-end tissues.

Axial Vectors & Oxygenation of the Lethal Corner:
Room Air paO2 & Slow Intracapillary Blood Flow Velocity

Radial O2 vectors only supplying 20% of the oxygen to the venous end.

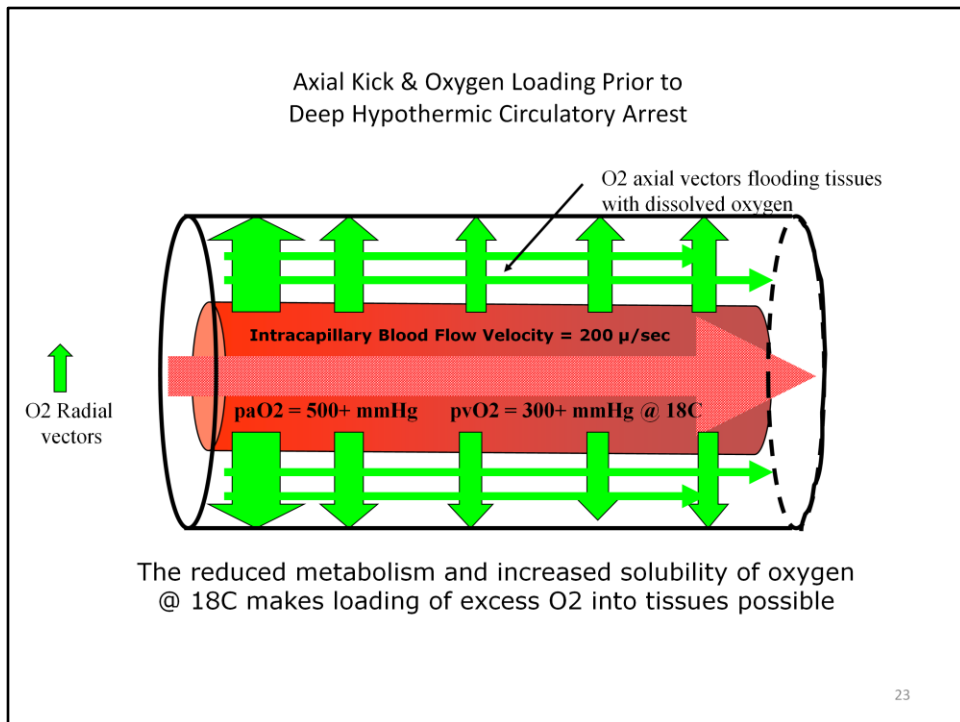Axial O2 vectors supplying 80% of the oxygen to the venous end.

During low flow states axial oxygen vectors may supply up to 80% of the oxygen entering the venous-end tissues of the Krogh cylinder.

When intracapillary blood flow velocity decreases (the cardiac index decreases), the hemoglobin releases more oxygen than normal resulting in a decreased venous hemoglobin oxygen saturation. The radial gradient of oxygen in the venous-end of the cylinder decreases and a lethal corner forms. At the same time, due to the decrease in the venous-end tissue oxygen concentration, the axial gradient increases and more oxygen moves from the arterial-end tissues to the venous-end tissues in an attempt to compensate for the reduced venous radial gradient. In this reduced blood flow scenario the source of oxygen entering the venous-end tissues is only 20% from radial vectors and 80% from axial vectors. That's not to say that adequate amounts of oxygen are entering the venous-end tissues during low blood flow. Rather that whatever limited supply of oxygen is coming into the venous end comes mostly from axial vectors.

Axial Vectors & Oxygenation of the Lethal Corner:
Hyperoxia & Slow Intracapillary Blood Flow Velocity
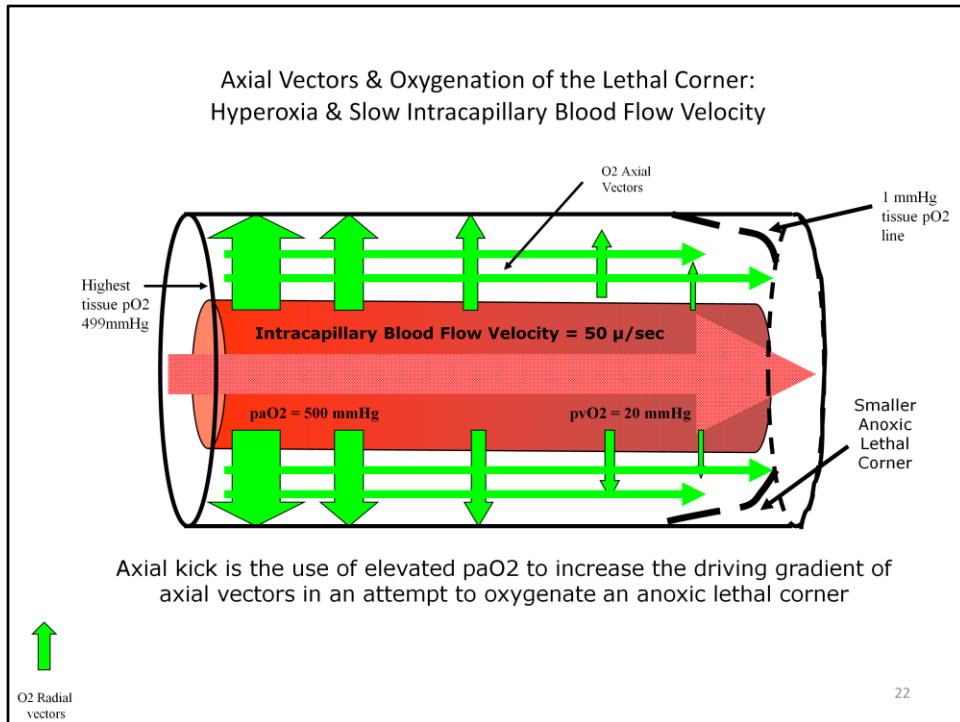
Hyperoxia does not significantly increase the oxygen content of arterial blood, but it does help to redistribute oxygen to lethal corner areas along axial vectors during period of low blood flow or poor PCD.
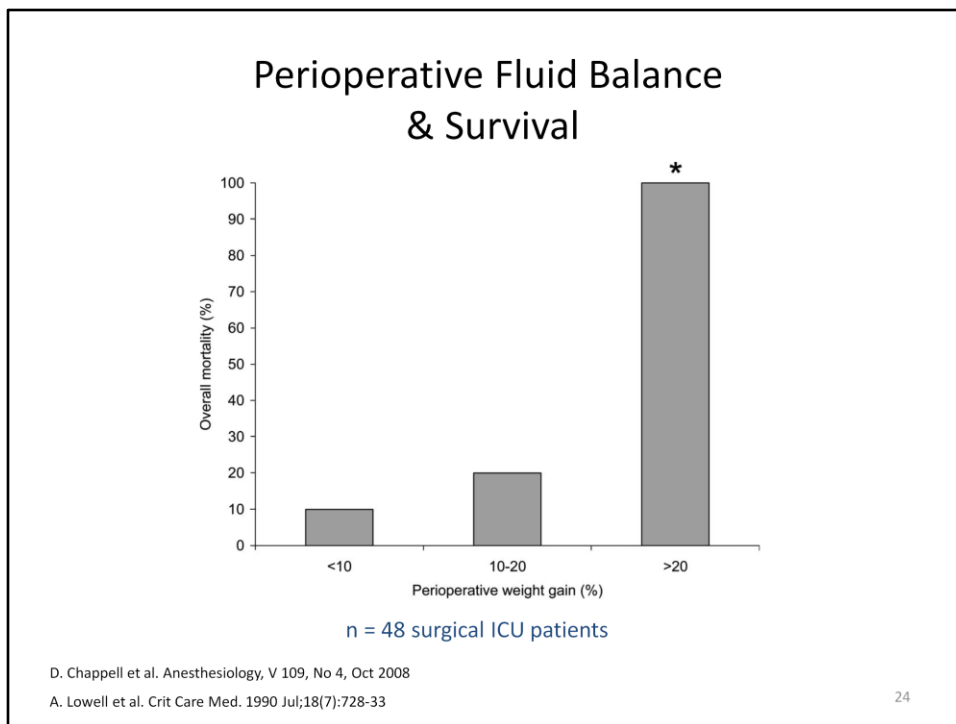
   The perfusionist who understands this axial vector phenomenon can compensate somewhat for pathologic or iatrogenic low flow states by increasing the pO2 of the arterial blood. For example, increasing the arterial pO2 from 80 to 500 mmHg floods the arterial-end tissues with oxygen and increases the axial gradient. This increased axial gradient then results in axial vectors that can extend into the lethal corner area, helping to suppress the formation of an anoxic lethal corner until blood flow can be restored. For example, during cardiopulmonary bypass or ECMO the blood flow may be lowered temporarily to facilitate a certain surgical or medical procedure. During this time period the patient may benefit from having the oxygenator sweep gas FiO2 increased to 100% to augment axial oxygen vectors. However this is only a temporary solution to a low blood flow condition. As discussed previously, if intracapillary velocity or PCD is decreased for too long a hypercapnic lethal corner can result.

Axial Kick & Oxygen Loading Prior to
Deep Hypothermic Circulatory Arrest

O2 axial vectors flooding tissues
with dissolved oxygen

Intracapillary Blood Flow Velocity = 200 μ/sec

paO2 = 500+ mmHg   pvO2 = 300+ mmHg @ 18C

O2 Radial
vectors

The reduced metabolism and increased solubility of oxygen
@ 18C makes loading of excess O2 into tissues possible

Hyperoxygenation prior to DHCA floods the tissues with dissolved oxygen and extends the safe arrest time before anaerobic metabolism starts.

The technique of deep hypothermic circulatory arrest (DHCA) is a good example of how PCD changes and how those changes can effect perfusion strategy. Patients survive hypothermic arrest procedures because of the reduced metabolic rate and reduced oxygen consumption, but there is a limit to how long this arrest period can last without damage. By stopping blood flow through the capillaries during DHCA, the capillary-to-cylinder ratio infinitely increases so that PCD is essentially zero. With virtually no flowing blood to supply the tissue cylinders, the entire body becomes one large Krogh cylinder containing a potentially huge lethal corner. At 18 °C, cerebral oxygen consumption is only about 20% of normal. Also oxygen is about 2/3rds more soluble (0.05 cc/mmHg/kg of H2O) at 18 °C than at 37 °C (0.03 cc/mmHg/kg of H2O). By taking advantage of the increased solubility of oxygen and the reduced oxygen requirements at 18 °C, dissolved oxygen can be stored in the very tissues where it will be used during the arrest period; not just on the hemoglobin in the blood but in the Krogh cylinders themselves. The tissue cylinders are flooded with oxygen during cooling using a high FiO2 to augment both radial and axial vectors so that all the tissues within the capillary bed are saturated just prior to DHCA. The use of axial vectors to flood a potential lethal corner with oxygen is known as "axial kick". An increase in the venous pO2 during cooling is indicative of the relative level of tissue oxygen loading. Reaching a venous pO2 greater than of 300 mmHg may be a more important parameter indicating when to initiate DHCA than simply reaching the target temperature or cooling for an arbitrary minimum time period.

The development of neurological pathology after cardiopulmonary bypass with DHCA has been associated with shorter cooling periods. Supposedly a cooling time that is too short causes uneven cooling of the brain tissue even if the target temperature is reached, resulting in brain damage during the arrest period. However an equally plausible explanation is that longer cooling periods allow for increased storage of oxygen in the tissues. By having more oxygen on board prior to DHCA, the tissues can better tolerate extended periods without circulation. An increased level of dissolved oxygen in the tissues would extend the time before anaerobic metabolism begins. Once anaerobic metabolism starts, intracellular pH worsens due to the production of lactic acid. This sets up a situation where re-oxygenation of the tissues can result in reperfusion injury when circulation is restored.

Perioperative Fluid Balance & Survival

n = 48 surgical ICU patients

D. Chappell et al. Anesthesiology, V 109, No 4, Oct 2008

A. Lowell et al. Crit Care Med. 1990 Jul;18(7):728-33

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Perioperative weight gain caused by edema is associated with increased morbidity and mortality; a weight gain > 20% of the body weight being uniformly fatal. Pulmonary edema can result in circulatory and respiratory failure. Cerebral edema can result in brain damage. Whole body edema can result in multiple organ failure. The increased morbidity and mortality associated with edema can be related to changes in the oxygen pressure field caused by a reduction in perfused capillary density.
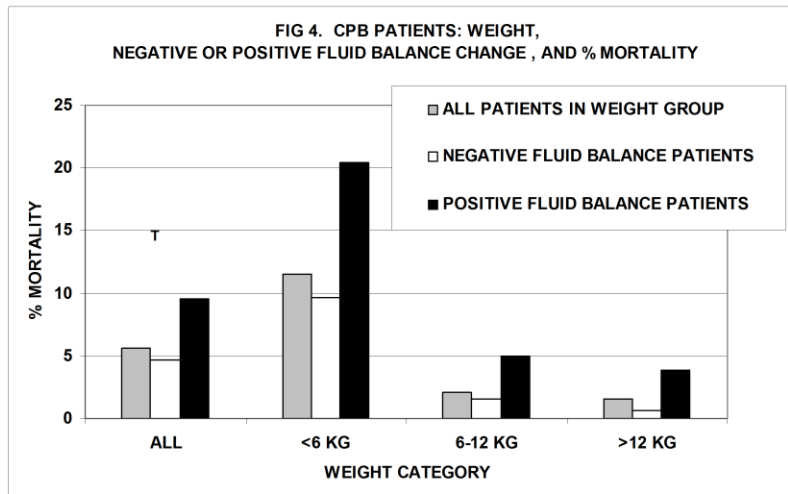
CMH 2003-2009: CPB Fluid Balance By Weight Vs. Mortality

[n = 1540, MORTALITY = 5.65%]

80% NEGATIVE BALANCE   20% POSITIVE BALANCE
MORTALITY = 4.6%   MORTALITY = 9.5%

FIG 4. CPB PATIENTS: WEIGHT, NEGATIVE OR POSITIVE FLUID BALANCE CHANGE , AND % MORTALITY

Fluid balance at the end of cardiopulmonary bypass (CPB) correlates to mortality. Acting as its own control, this population of 1540 CPB patients, some adults but mostly pediatric, has a mortality just over 5%. Eighty per cent of the patients had zero or negative fluid balances at the end of CPB and 20% had positive balances. Patients with a positive balance had a mortality of 9.5%, twice as high as those with a zero or negative balance at 4.6%. Infants (<6 KG) had an overall mortality of 11.3% with positive balance patients having twice the mortality as negative balance patients.
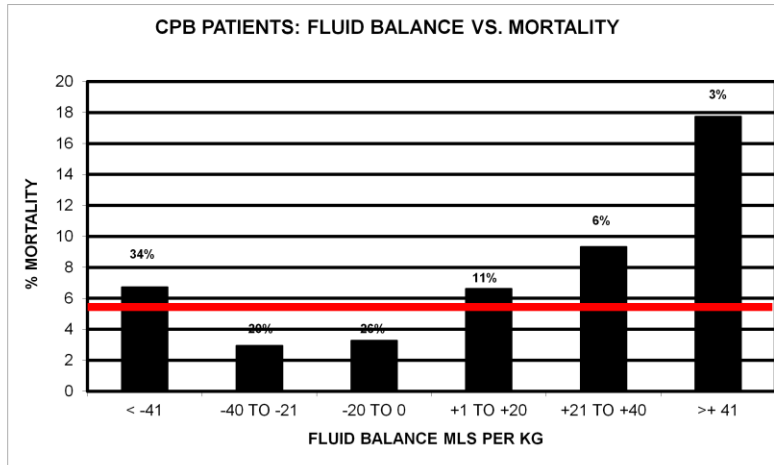
As the patient size and age increased, overall mortality fell. However larger patients with positive balances had 4 to 6 times the mortality as their negative balance counter-parts. The reason for this discrepancy compared to the infant group is unknown. But it is obvious that large patients with a positive fluid balance have a greater sensitivity to fluid overload than do infants and large patients with a negative balance.

CMH 2003-2009: CPB Fluid Balance Magnitude Vs. Mortality
[n = 1540, MORTALITY = 5.65%]

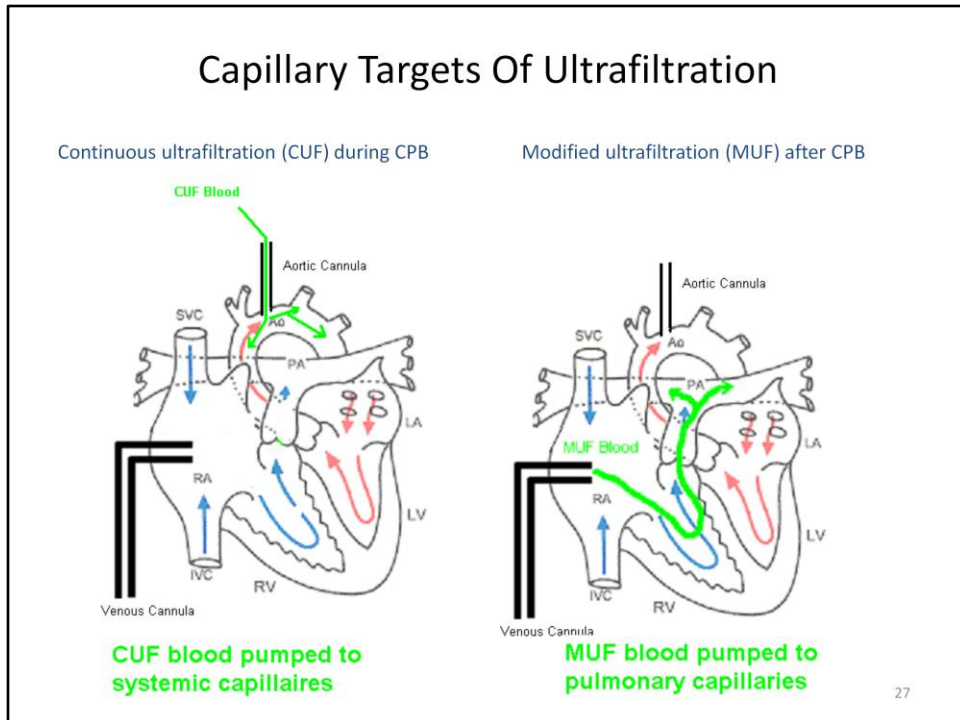80% NEGATIVE BALANCE   20% POSITIVE BALANCE
MORTALITY = 4.6%   MORTALITY = 9.5%

CPB PATIENTS: FLUID BALANCE VS. MORTALITY

% MORTALITY (y-axis: 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20)

Bars by FLUID BALANCE MLS PER KG:
- < -41 : 34%
- -40 TO -21 : 20%
- -20 TO 0 : 26%
- +1 TO +20 : 11%
- +21 TO +40 : 6%
- >+ 41 : 3%

FLUID BALANCE MLS PER KG

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   The magnitude of the fluid balance at the end of cardiopulmonary bypass (CPB) correlates to the magnitude of mortality. Patients with zero or negative balances of 0 to -40 mls/kg have the best survival. Patients can tolerate fluid removal up to -40 mls/kg (46% of the population) and still maintain a low mortality rate because excess fluid from congestive heart failure, preoperative fluid rehydration and sometimes preoperative fluid resuscitation can easily be removed without compromising the circulating blood volume. Patients with negative balances greater than -40 mls/kg (34% of the population) may have had too much fluid removed causing overt hypovolemia in the post operative period. This may have necessitated fluid resuscitation causing the mortality rate to rebound to a higher level.
   Patients with positive balances have steadily increasing mortality correlating as the amount of the retained fluid increases. Patients with positive balances exceeding +40 mls/kg have a mortality of 17.7%. Fortunately this category only comprises 3% of the population.

Capillary Targets Of Ultrafiltration

Continuous ultrafiltration (CUF) during CPB — Modified ultrafiltration (MUF) after CPB

CUF blood pumped to systemic capillaires
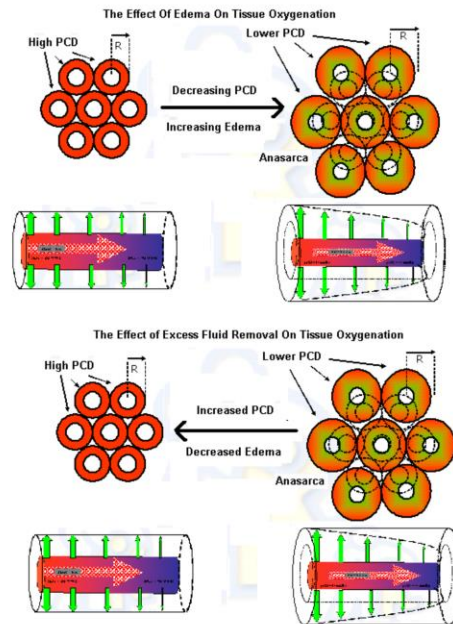
MUF blood pumped to pulmonary capillaries

There are two different capillary beds which the perfusionist can target for ultrafiltration. The application of ultrafiltration to each of the target beds gives different physiologic results.

During CPB, continuous ultrafiltration removes fluid from the blood passing through the circuit, concentrating the plasma proteins. Then it is returned to the patient's systemic circulation via the aorta. The blood entering the aorta has a slightly higher oncotic pressure (colloid osmotic pressure) than the rest of the body. Because large plasma proteins cannot easily pass through the capillary walls, the arterial blood's higher oncotic pressure tends to pull fluid from the tissues where it is removed by the systemic capillary blood flow, thus reducing systemic organ and peripheral edema. If the ultrafiltration is too aggressive, the patient's circulating blood volume is reduced too rapidly causing hypovolemia resulting in inadequate perfusion. This necessitates the administration of IV fluids, negating the benefits of continuous ultrafiltration.

During MUF, ultrafiltration removes volume from the residual CPB circuit volume which increases its oncotic pressure. This high oncotic blood is then directed into the right atrium where it mixes with the patient's blood prior to entering the pulmonary artery. This mixed blood enters the pulmonary artery with a slightly higher oncotic pressure than the rest of the body, pulling fluid from the pulmonary tissues where it is removed by the pulmonary capillary blood flow. This reduces pulmonary edema.
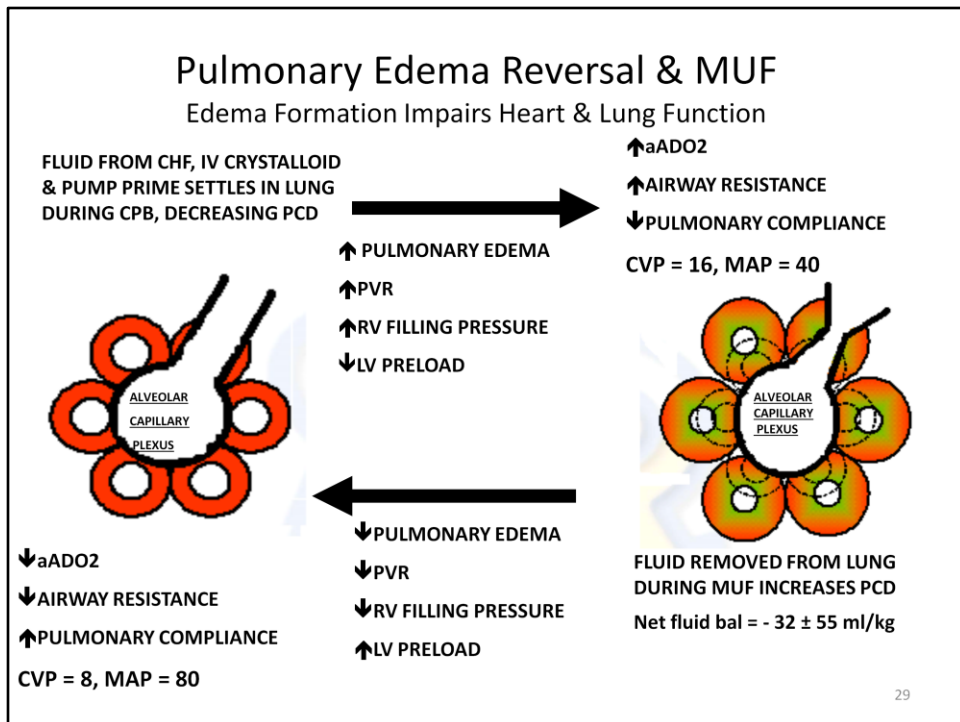
Severe edema or anasarca pushes the capillaries apart and reduces PCD. This results in reduced tissue oxygen concentration and the potential development of an anoxic lethal corner.

Many patients require extensive fluid resuscitation at some point during their treatment and will often develop massive edema (anasarca). Edema increases the extravascular tissue volume and pushes capillaries further apart. This mechanical separation decreases PCD which disrupts the oxygen pressure field (the radius of the Krogh cylinders increases). Anasarca can impact most of the soft tissues and organ systems and is frequently associated with progressive organ failure. This organ failure might be caused by a lethal corner that forms as a result of the disrupted oxygen pressure field even though the capillaries are open and carrying blood. An edematous heart, even though it is well perfused, may lack strength and endurance because of the decreased tissue oxygen concentration.

Diuresis or ultrafiltration can reduce systemic edema and bring capillaries closer together, restoring the oxygen pressure field to a more survivable configuration.

Pulmonary Edema Reversal & MUF
Edema Formation Impairs Heart & Lung Function

FLUID FROM CHF, IV CRYSTALLOID & PUMP PRIME SETTLES IN LUNG DURING CPB, DECREASING PCD

⬆aADO2
⬆AIRWAY RESISTANCE
⬇PULMONARY COMPLIANCE

CVP = 16, MAP = 40

⬆ PULMONARY EDEMA
⬆PVR
⬆RV FILLING PRESSURE
⬇LV PRELOAD

ALVEOLAR CAPILLARY PLEXUS

⬇aADO2
⬇AIRWAY RESISTANCE
⬆PULMONARY COMPLIANCE

CVP = 8, MAP = 80

⬇PULMONARY EDEMA
⬇PVR
⬇RV FILLING PRESSURE
⬆LV PRELOAD

FLUID REMOVED FROM LUNG DURING MUF INCREASES PCD

Net fluid bal = - 32 ± 55 ml/kg

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Edema in the pulmonary system can also result in a decreased PCD that moves the capillaries away from gas exchange near the lung alveoli and increases the vascular resistance to blood flow. This commonly occurs during cardiopulmonary bypass at a time when the lungs do not receive adequate perfusion via the pulmonary artery.

Interstitial edema increases pulmonary vascular resistance, right ventricular filling pressures and impairs right heart function. This is followed by a reduced left ventricular preload and subsequent fall in cardiac output. Commonly the treatment is to administer additional fluid to boost right heart output. This may provide temporary improvement in the cardiac output, but the additional fluid can worsen the pulmonary edema as well. In this example, an infant weans from CPB with a central venous pressure of 16 mmHg and a mean blood pressure of 40 mmHg. The airway is also compromised by reduced pulmonary compliance, increased airway resistance and increased oxygen requirements (increased aADO2) to achieve an adequate arterial oxygen saturation.

Combating the edema with targeted ultrafiltration can quickly reduce the pulmonary edema and restore normal pulmonary circulation and function. MUF removes an average of 32 ml/kg of fluid from infants, in our experience. This is a significant amount of fluid considering that the blood volume of an infant is only about 100 ml/kg. But since much of the fluid removed comes from the edematous lungs and peripheral tissues, cardiac function actually improves despite the net fluid removal.

Continuing with this example, the central venous pressure falls to 8 mmHg as fluid is removed and the mean arterial pressure increases to 80 mmHg. The drop in CVP is not just indicative the fluid removed, but is rather a reflection of the improved right heart function due to the reduced pulmonary edema. As right heart function improves, left heart preload improves resulting in an increase in blood pressure.

Infant MUF

- 1/5: MUF blood flow / venous return to the lungs
  - 100 cc/min MUF flow : 500 cc/min CO
    - High oncotic MUF blood combines with right heart blood
    - Higher oncotic blood goes directly to the lungs
    - Higher oncotic blood drags water (edema) from lung interstitium
    - Improved pulmonary and hemodynamic function
  - Typically 5-10% hematocrit increase
  - Increase in plasma protein and clotting factor concentration w/o increasing blood volume

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MUF is known to improve post-CPB hemodynamics in infants and children. Some perfusionists speculate that this effect occurs because MUF removes inflammatory mediators from the blood. However, the explanation is probably much simpler. MUF increases the plasma proteins in the residual circuit blood and combines it with the patient's blood in the right atrium. This high oncotic blood goes directly to the lungs where it removes interstitial pulmonary fluid by osmosis. This modifies the pulmonary vascular bed to such as degree that hemodynamics quickly improve.

Additional benefits of MUF include an increase in the plasma proteins, clotting factors and hematocrit without increasing the circulating blood volume. The key to obtaining these benefits lies in the ratio of the amount of MUF blood flow to the patient's right atrial venous return flow. In an infant, the MUF blood flow is about 1/5th of the patient's total cardiac output. As a result the oncotic pressure of the combined blood volumes is high. As the patient increases in size, this ratio changes and the benefits are reduced.

Adult MUF

- 1/20: MUF blood flow / venous return to the lungs
    - 200 cc/min MUF flow : 4000 cc/min CO
        - High oncotic MUF blood diluted by right heart blood
        - Relatively low oncotic blood goes to the lungs
        - No oncotic drag to remove water (edema) from lung interstitium
        - Pulmonary benefits negligible
    - Typically 1- 4% hematocrit increase
    - Small increase in clotting factors w/o increasing blood volume

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In an adult, the relationship between the MUF blood flow and the patient's total cardiac output may be 1/20, rather than 1/5. So the oncotic pressure increase of the pulmonary artery blood is much less than during infant MUF. Therefore there is less oncotic pressure to remove fluid from the lungs. As a result, there are negligible pulmonary benefits. Typically the increases in clotting factors and hematocrit are also small. Therefore the benefits of MUF in adults may not be worth the time required to perform the procedure.

Improving Pulmonary Effects In Adult MUF

- After CPB, patient osmolarity = 300 mosmoles
- Residual circuit volume = 1 L @ 300 mosmoles
- Add 50 mEq/L NaHCO3 or 2 gm mannitol to circuit
  - Increases residual circuit fluid osmolarity to 400 mosmoles/L
    - Add NaHCO3 or mannitol to chase fluid

- 200 mls/min MUF blood (400 mosmoles/L) + 4000 mls/min patient blood (300 mosmoles/L)
- Pul. artery blood osmolarity increases from 300 to 305
- Osmotic drag removes 67 mls/min fluid lung interstitium
- Removes 335 mls from lungs in 5 minutes of MUF

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However it is possible to improve the pulmonary and hemodynamic effects of MUF in adults by increasing the osmolarity of the residual CPB circuit volume. MUF increases the oncotic pressure in the infant's pulmonary artery by hemoconcentrating the residual circuit plasma proteins. However in the adult this could only be accomplished by adding multiple vials of 25% albumin to the residual circuit volume. A better strategy is to increase the osmotic pressure of the pulmonary artery blood. Oncotic pressure is exerted by large, protein molecules. Osmotic pressure is exerted by much smaller but more abundant molecules, usually ions (electrolytes) or sugars. The difference is that the small molecules eventually equilibrate on both sides of the capillary membrane whereas the protein molecules mostly remain within the capillary lumen.

Adding 50 mEq of NaHCO3 or 2 gm of mannitol to each liter of residual circuit volume will increase the osmotic pressure enough so that when the residual circuit volume is mixed 1/20 with the patient's right atrial circulating blood volume, the osmotic pressure will be high enough to remove excess interstitial pulmonary edema. In the example above, the fluid removed from the lungs by increasing the osmotic pressure of the pulmonary artery blood by only 5 milliosmoles can be calculated at 67 mls/min during 5 minutes at a MUF blood flow of 200 mls/min, for a total of 335 mls removed from the lungs. This method can remove enough lung water to improve hemodynamics and possibly avoid the excessive use of cardiac drugs, diuretics or even mechanical support postoperatively.

Quantifying The Lethal Corner

- The size of the lethal corner can be indirectly measured.

- The quantitative assessment of the lethal corner can be used to:

  - Determine the potential for reperfusion injury
  - Time extracorporeal intervention
  - Predict survival

The Krogh cylinder does not exist as an actual anatomical structure; it is only a model that can be used to explain the oxygen pressure field. The lethal corner is also only a theoretical concept within the model. However as perfused capillary density changes, inadequately perfused tissues can become anoxic and hypercapnic. An indirect clinical measurement of the magnitude of the of these inadequately perfused tissues (the lethal corner) can be made using common and routine laboratory tests. The quantitative assessment of the lethal corner can be useful in many ways; assessing the potential for reperfusion injury, timing extracorporeal intervention, assessing the effectiveness of extracorporeal intervention, and predicting survival. That discussion is continued in Session 2.

OPFT: Summary

- New insight for perfusionists
- Helps to design successful perfusion strategies
- Goal to achieve favorable outcomes

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Knowledge of how the oxygen pressure field works can provide new insight to the perfusionist utilizing short term or long term extracorporeal support.   This understanding of vital gas exchange at the microvascular level helps perfusionists to design successful perfusion strategies more apt to result in favorable outcomes for patients.

END OF SESSION 1
REFERENCES

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1. Krogh A. The rate of diffusion of gases through animal tissues with some remarks on the coefficient of invasion. J Physiol Lond 1918; 52:391-408.
2. Krogh A. The number and distribution of capillaries in muscles with calculation of the oxygen pressure head necessary for supplying the tissue. J Physiol Lond 1918; 52:409-415.
3. Kreuzer F. Oxygen supply to tissues: the Krogh model and its assumptions. Experientia 1982; 38(12):1415-26.
4. Lubbers D. Fundamentals and significance of local oxygen pressure measurements and pO2 histograms in the evaluation of oxygen supply to organs and organisms. In: Ehrly, AM, editor. From Determination Of Tissue Oxygen Pressure In Patients. pages 1-13. Oxford, New York: Pergamon Press, 1983.
5. Lund N. Skeletal muscle surface oxygen pressure fields in normal human volunteers and in critically ill patients. In: Ehrly AM, editor. Determination Of Tissue Oxygen Pressure Fields In Patients. Oxford, New York: Pergamon Press; p 53-59, 1983.
6. Popel AS. Theory of oxygen transport to tissue. Crit Rev Biomed Eng 1989; 17(3):257-321.
7. Schumacker PT, Samsel RW. Analysis of oxygen delivery and uptake relationships in the Krogh tissue model. J Appl Physiol 1989; 67(3):1234-44.
8. Hugot P, Sicsic JC, Schaffuser A, et al. Base deficit in immediate postoperative period of coronary surgery with cardiopulmonary bypass and length of stay in intensive care unit. Intensive Care Med 2003; 29(2):257-61.
9. Murray DM, Olhsson V, Fraser JI. Defining acidosis in postoperative cardiac patients using Stewart's method of strong ion difference. Pediatr Crit Care Med 2004; 5(3):240-5.
10. Johnson BA, Weil MH. Redefining ischemia due to circulatory failure as dual defects of oxygen deficits and of carbon dioxide excesses. Crit Care Med 1991; 19(11):1432-8.
11. McCullough JN, Zhang N, Reich DL, et al. Cerebral metabolic suppression during hypothermic circulatory arrest in humans. Ann Thorac Surg 1999; 67(6):1895-9; discussion 1919-21.
12. Merino C. Formulas for temperature PaO2 correction. Anesth Analg 1999; 89(4):1065.
13. Pearl JM, Thomas DW, Grist G, et al. Hyperoxia for management of acid-base status during deep hypothermia with circulatory arrest. Ann Thorac Surg 2000; 70(3):751-5.
14. Gaynor JW, Nicolson SC, Jarvik GP, et al. Increasing duration of deep hypothermic circulatory arrest is associated with an increased incidence of postoperative electroencephalographic seizures. J Thorac Cardiovasc Surg 2005; 130(5):1278-86.
15. Wong PC, Barlow CF, Hickey PR, et al. Factors associated with choreoathetosis after cardiopulmonary bypass in children with congenital heart disease. Circulation 1992; 86(5 Suppl):II118-26.
16. Boldt J, Kling D, von Bormann B, et al. Extravascular lung water and hemofiltration during complicated cardiac surgery. Thorac Cardiovasc Surg 1987; 35(3):161-5.
17. Steinhorn DM. Termination of extracorporeal membrane oxygenation for cardiac support. Artif Organs 1999; 23(11):1026-30.
18. Grist G, Thomas D. Blood anion gaps and venoarterial carbon dioxide gradients as risk factors in long-term extracorporeal support. J Extra Corpor Technol 1997; 29(1):6-10.
19. Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M. A rational approach to perioperative fluid management. Anesthesiology 2008;109:723-40.
20. Lowell JA, Schifferdecker C, Driscoll DF, Benotti PN, Bistrian BR. Postoperative fluid overload: not a benign problem. Crit Care Med 1990;18:728-33.

Beyond Fick: Discussions On Advanced Perfusion Theory

Session 2: Viability Index Scoring For Critical Cardiopulmonary And Extracorporeal Support Patients

Gary Grist RN CCP

No Disclosures

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SESSION 2 TABLE OF CONTENTS

Objectives

1. Redefine shock in terms of the oxygen pressure field.

2. Describe the relationship between shock, anaerobic metabolism and intracellular retention of carbon dioxide.

3. Describe the relationship between anaerobic metabolism and the anion gap.

4. Describe the anoxic lethal corner.

5. Describe the relationship between intracellular carbon dioxide retention and the venoarterial CO2 gradient.

6. Describe the hypercapnic lethal corner.

7. Describe co-incident lethal corners.

8. Describe the relationship between the anion gap, the venoarterial CO2 gradient and the Viability Index.

9. Describe the quantification of the magnitude of shock and its relationship to the potential for reperfusion injury.

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This session will redefine shock in terms of the oxygen pressure field and describe the relationship between shock, anaerobic metabolism and intracellular retention of carbon dioxide. The anion gap can be used to quantify the extent of anaerobic metabolism and the anoxic lethal corner. The venoarterial CO2 gradient quantifies intracellular CO2 retention and the hypercapnic lethal corner. When co-incident lethal corners occur, the patient is at the greatest risk of death. Combining the scores for both anoxic and hypercapnic lethal corners results in a Viability Index which relates to the patient's risk of death from reperfusion injury even if immediate resuscitation is successful.

The Viability Index quantifies the magnitude of the shock state and delineates a cut-point beyond which the restoration of normal circulation (either by successful resuscitation or extracorporeal support) actually contributes to the patient's demise by causing a lethal reperfusion injury to the tissues. A patient who exceeds the cut-point may need a modified form of resuscitation that addresses the morbid ramifications of reperfusion injury.

What Is Shock?

   A patient develops shock when cardiopulmonary function is compromised by a variety of conditions: cardiac failure, hypovolemia, trauma, sepsis, central nervous system damage and acute respiratory distress syndrome being the most common causes. Several well known complicated and simple scoring systems have been used to assess the potential danger to the patient. The APACHE III (Acute Physiology, Age, Chronic Health Evaluation) system assesses more than 20 factors and produces a score of 0 – 299 (normal range = 14 to 102). The Shock Index system assesses only two factors (SI = heart rate/systolic blood pressure) and produces a score of 0 - 1 (normal range = 0.5 to 0.7). These scoring systems attempt to quantify the risk of dying. However, they fail to consider the potential danger of reperfusion injury after successful resuscitation.

   By traditional definition, shock is a medical emergency in which the body is not receiving an adequate flow of blood and oxygen, resulting in serious damage or death. There are three stages of shock. During Stage I (compensated) shock, the body draws on internal compensation mechanisms to maintain adequate perfusion. Medical intervention is most effective during this stage. In Stage II (decompensated) shock, internal compensation and medical intervention become less effective and the overt signs of under perfusion develop. In Stage III (irreversible) shock, internal compensation mechanisms and medical intervention completely fail. Organ failure and death is the final endpoint.
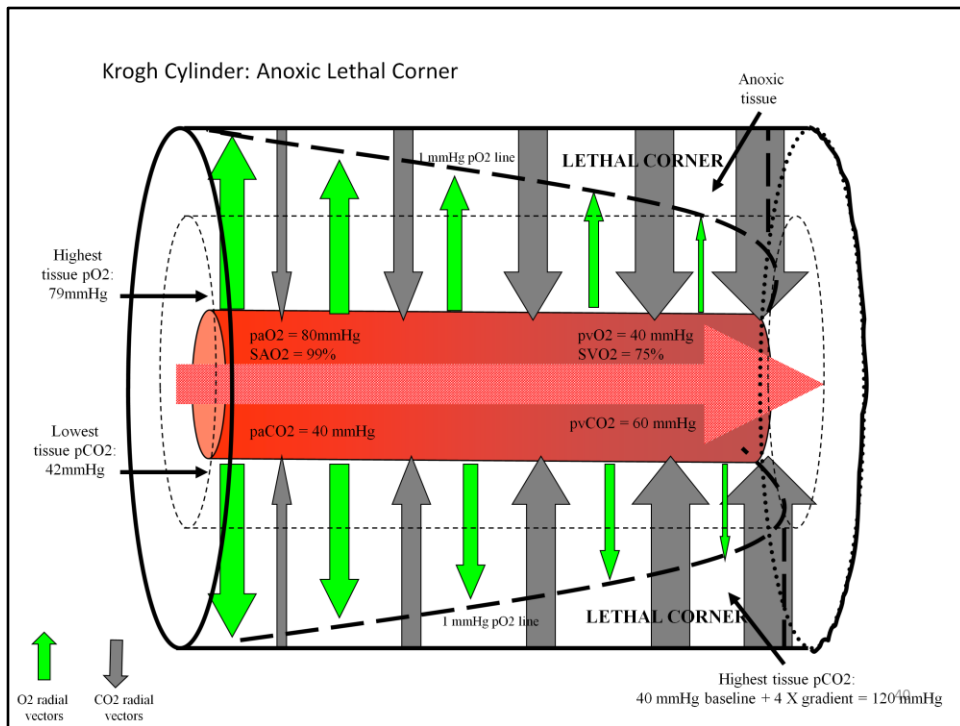
   The blood pressure, arterial oxygen saturation and even cardiac output can often be normalized in the shock patient by medical, clinical and even mechanical means without really improving shock at the cellular level. Since the Viability Index (VI) quantifies the magnitude of the shock state separately from monitored hemodynamic or oxygenation values, it can be used to separate those patients who genuinely respond to treatment from those patients whose transiently improved vital signs provide false reassurance of the resolution of shock. Furthermore, the VI delineates a cut point beyond which the restoration of normal circulation (either by successful resuscitation or extracorporeal support) actually contributes to the patient's demise by causing a lethal reperfusion injury to the tissues. A patient who exceeds the cut point may need a modified form of resuscitation that addresses the morbid ramifications of reperfusion injury.

Perfused Capillary Density (PCD)
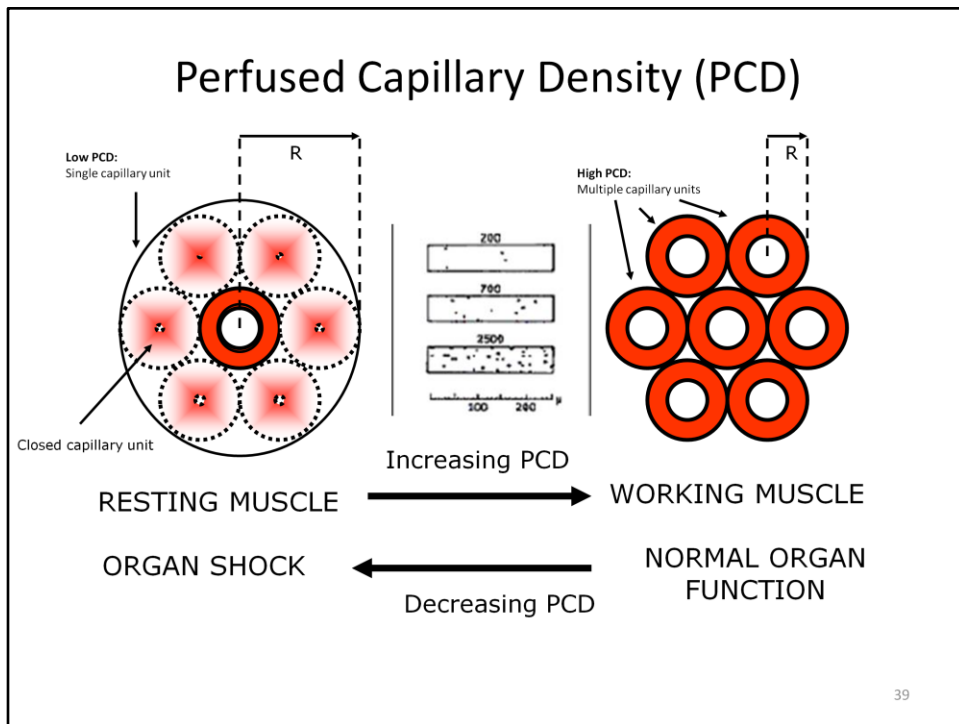
Perfused capillary density changes as the metabolic demands increase. Failure to increase PCD during times of stress is pathologic and is associated with the health state of the patient.

According to the Krogh model of the oxygen pressure field, perfused capillary density (PCD) is the most important variable in maintaining normal homeostasis. Normally PCD will change depending on the metabolic requirements of the surrounding tissue; increasing when metabolic needs increase and decreasing when metabolic needs decrease. The body's ability to open and close capillaries is the key to maintaining homeostasis in any type of tissue without excessive utilization of physiologic resources.

During illness additional capillaries may need to open to maintain homeostasis. But these additional capillaries may fail to open and those that were previously open may close, resulting in decreased PCD. This phenomenon has many etiologies such as cardiac failure, blood loss, infection, spinal nerve damage, etc. However they are all grouped under a common diagnosis called "shock". So another definition of shock is the failure of the body to open an adequate number of capillaries to supply oxygen and remove carbon dioxide. This can occur even in the presence of normal cardiac output and oxygen delivery. So in OPFT terms, shock is simply inadequate PCD, whatever the cause. Shock can surreptitiously occur even if cardiac output and oxygenation seem normal because PCD in vital organs cannot be quantified clinically using the customary assessments. When poor PCD occurs the patient is deemed to have a 'lethal corner'.

Krogh Cylinder: Anoxic Lethal Corner

Anoxic tissue

1 mmHg pO2 line   LETHAL CORNER

Highest tissue pO2: 79mmHg

paO2 = 80mmHg
SAO2 = 99%

pvO2 = 40 mmHg
SVO2 = 75%

Lowest tissue pCO2: 42mmHg

paCO2 = 40 mmHg

pvCO2 = 60 mmHg

1 mmHg pO2 line   LETHAL CORNER

O2 radial vectors   CO2 radial vectors

Highest tissue pCO2:
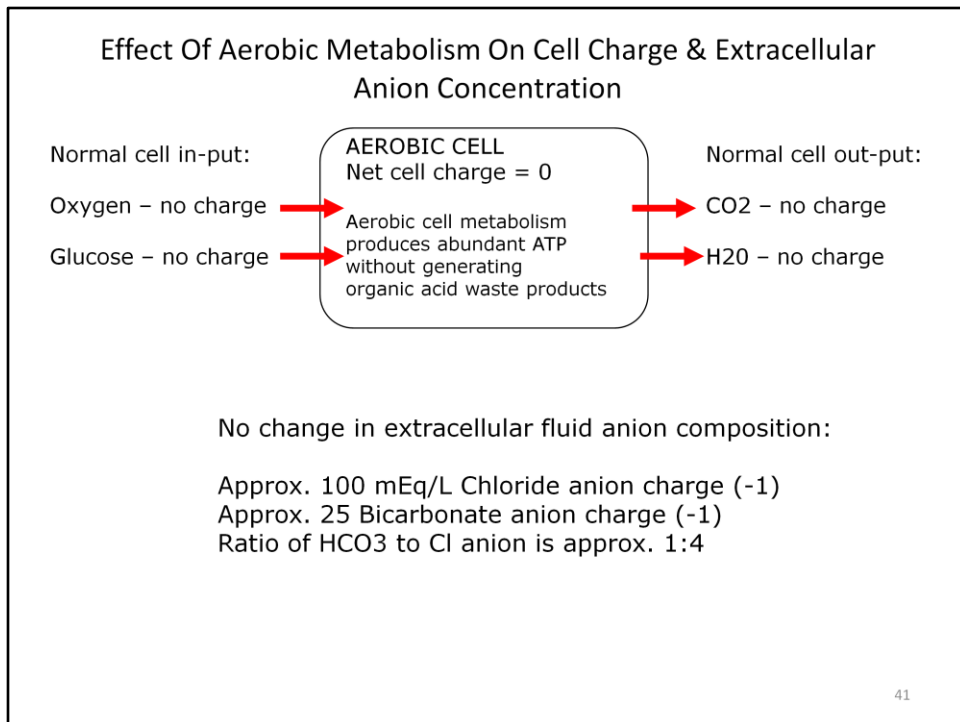40 mmHg baseline + 4 X gradient = 120 mmHg

A pathologic or iatrogenic decrease in PCD can result in the development of either an anoxic or a hypercapnic lethal corner or both, simultaneously.

When PCD is reduced without a concurrent reduction in metabolism or during an increased metabolic need, the Krogh model predicts the formation of a lethal corner. The presence of a lethal corner is the harbinger of severe physiologic distress. So detecting the presence of a lethal corner is vital. Theoretically a lethal corner can form even in the presence of normal Fick values.

The Krogh cylinder model seems to suggest that an anoxic lethal corner and a hypercapnic lethal corner should develop simultaneously. However in the clinical setting each can develop independently without the other being present. But the worst outcomes occur when they are both present at the same time.
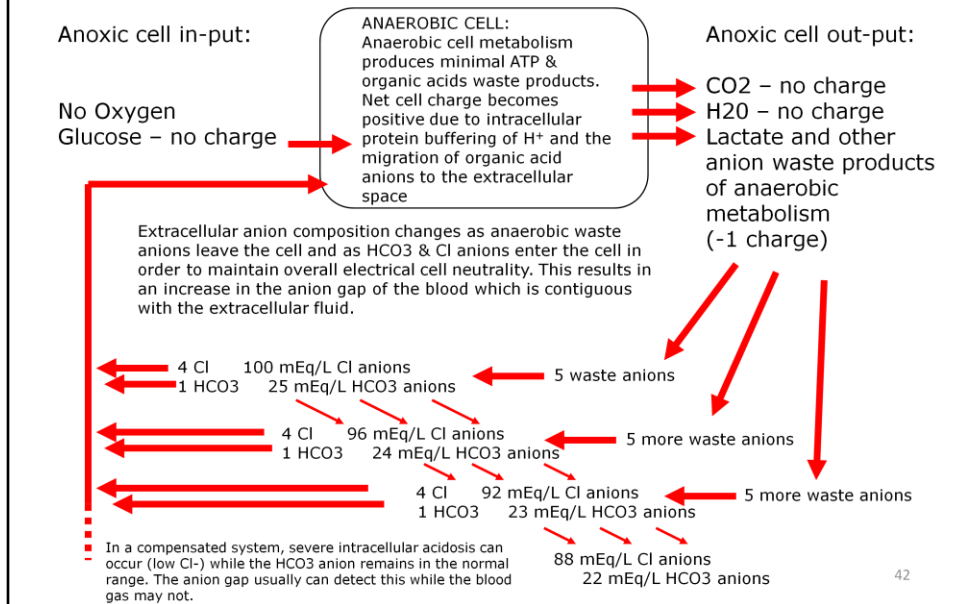
Effect Of Aerobic Metabolism On Cell Charge & Extracellular Anion Concentration

Normal cell in-put:

Oxygen – no charge

Glucose – no charge

AEROBIC CELL
Net cell charge = 0

Aerobic cell metabolism produces abundant ATP without generating organic acid waste products

Normal cell out-put:

CO2 – no charge

H20 – no charge

No change in extracellular fluid anion composition:

Approx. 100 mEq/L Chloride anion charge (-1)
Approx. 25 Bicarbonate anion charge (-1)
Ratio of HCO3 to Cl anion is approx. 1:4

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During aerobic metabolism cells take in oxygen and glucose and expel carbon dioxide and water while maintaining a neutral electrolytic cell charge.

   The perfusionist cannot always rely on the usual indicators like blood pressure and hemoglobin oxygen saturations for assurance that tissue perfusion is adequate because these variables can be easily manipulated into normal ranges by the perfusionist. This is what the perfusionist really needs to know; is the tissue perfusion suboptimal?
   The key in detecting an anoxic lethal corner lies in understanding what happens in anoxic cells at the capillary level. The normal cell takes in oxygen and glucose, undergoes aerobic metabolism, and excretes water and carbon dioxide. Neither the oxygen nor the glucose entering into the cell nor the carbon dioxide and water leaving the cell are ionic compounds. The routine entry and exit of these molecules do not affect the neutral ionic charge of the cell.

Effect Of Anaerobic Metabolism On Cell Charge & Extracellular Anion Concentration

Anoxic cell in-put:

No Oxygen
Glucose – no charge

ANAEROBIC CELL:
Anaerobic cell metabolism produces minimal ATP & organic acids waste products. Net cell charge becomes positive due to intracellular protein buffering of H$^+$ and the migration of organic acid anions to the extracellular space

Anoxic cell out-put:

CO2 – no charge
H20 – no charge
Lactate and other anion waste products of anaerobic metabolism (-1 charge)

Extracellular anion composition changes as anaerobic waste anions leave the cell and as HCO3 & Cl anions enter the cell in order to maintain overall electrical cell neutrality. This results in an increase in the anion gap of the blood which is contiguous with the extracellular fluid.

4 Cl   100 mEq/L Cl anions
1 HCO3   25 mEq/L HCO3 anions

5 waste anions

4 Cl   96 mEq/L Cl anions
1 HCO3   24 mEq/L HCO3 anions

5 more waste anions

4 Cl   92 mEq/L Cl anions
1 HCO3   23 mEq/L HCO3 anions

5 more waste anions

In a compensated system, severe intracellular acidosis can occur (low Cl-) while the HCO3 anion remains in the normal range. The anion gap usually can detect this while the blood gas may not.

88 mEq/L Cl anions
22 mEq/L HCO3 anions

42

In the anoxic cell, there is no oxygen available. The glucose enters the cell, undergoes anaerobic metabolism with the resultant waste products of water, carbon dioxide and organic acids such as lactic acid. The hydronium cation from the organic acid is chemically complexed to the intracellular protein buffers. However the organic acid anion, mostly lactate, is free to migrate outside of the cell.

In the extracellular fluid the electrolyte composition is very similar and contiguous with the blood serum electrolytes. In this example, there is an extracellular anion concentration that includes 100 mEq/L of the Cl$^-$ anion and 25 mEq/L of the HCO3$^-$ anion. The cell becomes positively charged by the hydronium cation which becomes chemically complexed to intracellular buffers while the negatively charged lactate ion migrates out of the cell. Subsequently an equivalent number of major extracellular anions must migrate intracellularly in order to maintain overall cell electrical neutrality. This has the effect of changing the composition of the major extracellular anions and disrupts the balance between the cations and anions in the extracellular fluid and blood serum. This disruption is quantified as an increased anion gap (AG); the difference between the total cation charge and the total anion charge.

An abbreviated formula for the AG subtracts the total of the 2 major anions (Cl and HCO3) from the major cation sodium (Na). This is the formula used for the values described herein:

Na mEq/L – (Cl mEq/L + HCO3 mEq/L) = anion gap mEq/L
Example from blood serum: 135 – (100 + 24) = 11

The normal range varies depending on the type of testing equipment used at each laboratory. All of the AG values described herein were tested using blood serum and ion selective electrodes. However there is a wide range of analyzers that can result in a wide variation of anion gap measurements. For example, whole blood tests for the anion gap are not equivalent to serum measurements because of interference by formed elements in the blood. Also many laboratories include the potassium as part of the calculation and may also use the total carbon dioxide instead of the bicarbonate level. For example, test results from a whole blood sample that uses potassium and total CO2 in the formula may be different from the serum test and formula drawn on the same patient. This is a different formula:

(Na mEq/L + K mEq/L) – (Cl mEq/L + TCO2 mEq/L) = anion gap mEq/L
Example from whole blood: (135 + 5) – (100 + 25) = 15

Albumin Correction Factor For The Anion Gap

Uncorrected Anion Gap mEq/L	Albumin gm/dl	Albumin Correction Factor	Albumin Corrected Anion Gap mEq/L
10	4	0	10
10	3	2.5	12.5
10	2	5	15
10	1	7.5	17.5

44

AG is a controversial number, but it is generally accepted that a severely elevated anion gap value has good positive predictive value for complications and mortality and represents an indirect method of assessing a change in intracellular pH. However its predictive value can be further enhanced by making two primary corrections; one for serum albumin concentration and one for renal function (blood urea nitrogen = BUN).

Albumin is a negatively charged molecule and 4 gm/dl adds about 10 mEq/L to the AG value. So each gm/dl of albumin contributes 2.5 mEq/L to the AG. If the albumin is abnormally low the AG will read erroneously low. For each gm/dl that the albumin is below 4 mEq/L, 2.5 mEq/L needs to be added to the AG value. The table illustrates how the albumin correction can be applied.

BUN vs. Anion Gap and Corrected Anion Gap

Off ECMO @ 138 Hours

Pt. #245 peri-ECMO hours
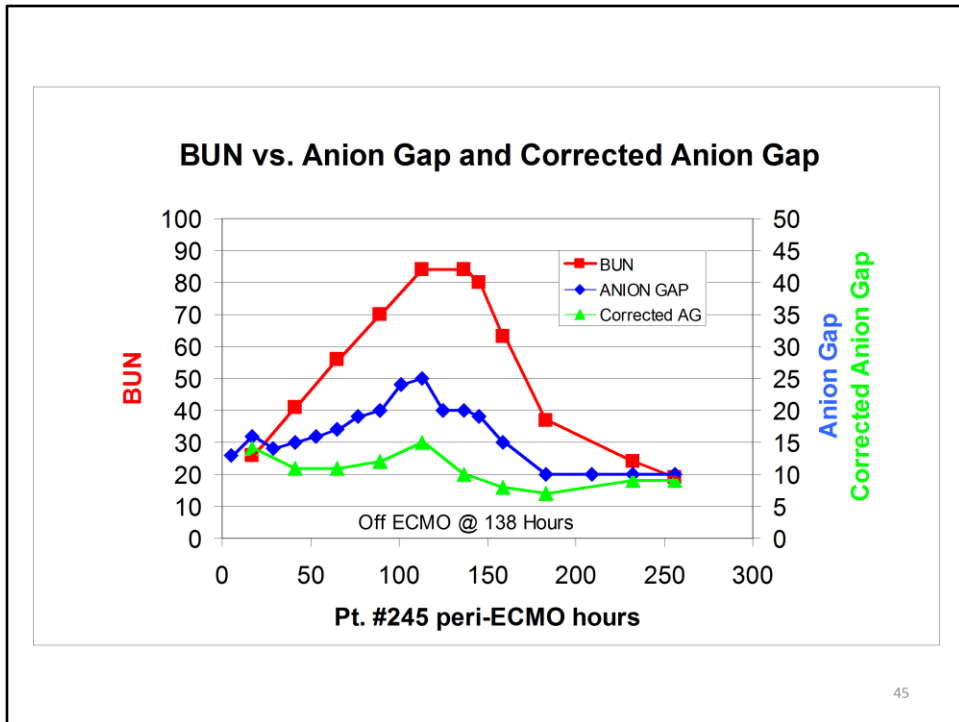
Example of an ECMO patient whose renal failure caused a BUN increase. The anion gap increased correspondingly into a lethal range. The application of the BUN correction factor reveals much lower and safer anion gap values.

During renal failure organic acids normally cleared by the kidneys are retained in the blood. These acids do not reflect a life threatening alteration in the intracellular milieu the way that lactic acid does. However they do increase the AG. The quantity of these retained 'renal acids' is roughly proportional to the increase in the blood urea nitrogen (BUN). This is an example of an ECMO patient whose renal failure caused the BUN to increase to 85 mg/dl. At the same time, the AG also peaked at the seemingly near lethal level of 25 mEq/L. However applying the BUN correction factor lowered the AG to only 15 mEq/L, much less indicative of a lethal intracellular pH change.

To apply the BUN correction factor, for every 7 mg/dl that the BUN goes above 15 the AG should be reduced by 1 mEq/L. However once the BUN exceeds 71 mg/dl, the correction factor becomes unreliable and no further AG correction should be made.

BUN Correction Factor For The Anion Gap

Uncorrected Anion Gap mEq/L	Blood Urea Nitrogen (BUN) mg%	BUN Correction Factor	BUN Corrected Anion Gap mEq/L
10	15	0	10
11	22	-1	10
12	29	-2	10
13	36	-3	10
14	43	-4	10
15	50	-5	10
16	57	-6	10
17	64	-7	10
18	71	-8	10
Make no further correction if BUN exceeds 71 mg%.			

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The BUN correction factor for the AG was determined by multiple observations in almost 300 ECMO patients. This table illustrates how the BUN correction factor can be applied. The corrected anion gap (AGc) is the number resulting from the application of the albumin and BUN correction factors to the normal AG measurement. These corrections improve the predictive power of the AG and make it a valuable tool for perfusionists attempting to assess for the presence of an anoxic lethal corner.

The AGc has the advantage over lactate measurements in that peak lactate values often lag behind the peak AGc by about 2 hours. So decisions concerning effective interventional strategies can be made sooner if the AGc is serially monitored.

CPB, ECMO, The Corrected Anion Gap (AGc),
And Survival

- The validity of the AGc to predict survival can be easily confirmed in CPB AND ECMO patients.
- The AGc in CPB and ECMO patients is more predictive than diagnosis.
- The AGc is not predictive in the presence of a lethal anatomy.

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   The assessment value of the AGc can be applied to extracorporeal support patients, particularly ECMO patients who are ideal subjects for the observational study of the oxygen pressure field. ECMO patients require maximum medical support prior to ECMO. They are then rescued from death at the last moment by placing them on a heart/lung pump. This is followed by frequent lab testing to monitor their progress. If the lethal corner really exists and can be detected, the best place to search for it is in ECMO patients.
   The great variety of diagnoses in ECMO patients tests the theory that a large lethal corner (rather than a specific diagnosis) is the primary cause of severe complications and death, in the absence of a lethal anatomy. For example, patients with meconium aspiration syndrome (MAS) have a 94% national survival rate on ECMO. Only those MAS patients with a lethal corner should experience a severe complication or death. A review of 45 patients undergoing ECMO for MAS at Children's Mercy Hospitals and Clinics (CMH) in Kansas City, Missouri, demonstrated 43 survivors and 2 expired patients (95.5% survival). Only the two expired patients had elevated AGc values averaging 20 mEq/L during the ECMO treatment. In another example, group B streptococcus (GBS) septicemia patients have a national survival rate of only 77% on ECMO. Of 15 GBS patients at CMH there were 2 non-survivors (86.7% survival) and they both had average AGc values exceeding 20 mEq/L. As illustrated by these two examples, an elevated AGc value is more predictive of poor outcome than the diagnosis in ECMO patients who do not have a lethal anatomical defect.

First Corrected Anion Gap In PICU After CPB: Correlation To Survival

% Mortality

AG < 15 mEq/L — AG 15-19 mEq/L — AG 20-24 mEq/L — AG =/> 25 mEq/L

CMH survival to discharge vs. 1ST corrected anion gap after CPB, $p < 0.05$

48
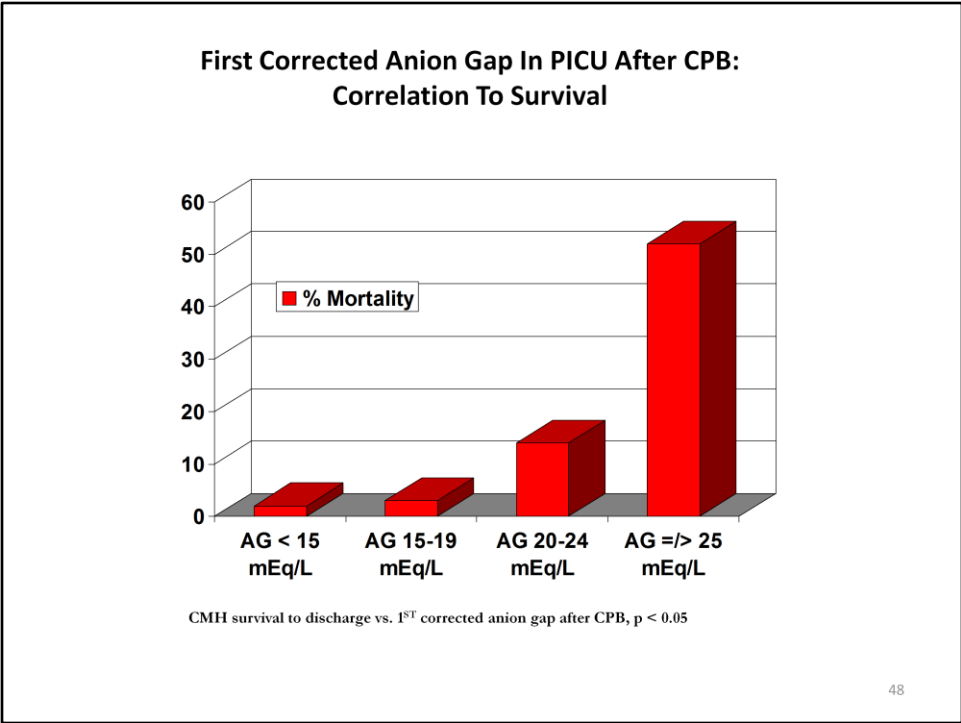
\In the post operative period after congenital heart surgery, the initial AGc is indicative of how well the patient tolerated the surgery. Subsequent measurements indicate if the patient is improving or worsening. This chart illustrates the predictive capacity of the 1st corrected anion gap (AGc) measured in the ICU after congenital heart surgery. The higher the post operative AGc the greater the mortality. Patients with a normal AGc (< 15 mEq/L) have less than 1% mortality and those with a AGc of 25 mEq/L or higher have a mortality greater than 50%. The AGc quantifies tissue hypoxia independently of other physiologic and hemodynamic assessments. Lactates used to assess the adequacy of tissue oxygenation often peak several hours after the maximum AGc. Waiting for lactate levels to reach the *LD50 can delay the implementation of effective extracorporeal intervention.

 * The lethal dose level at which 50% of the patients die. For lactate the value is about 11 mmol/L. If the normal range for the anion gap is 7-14 mEq/L, a lactate of 11 mmol/L would increase the anion gap to 18-25 mEq/L.
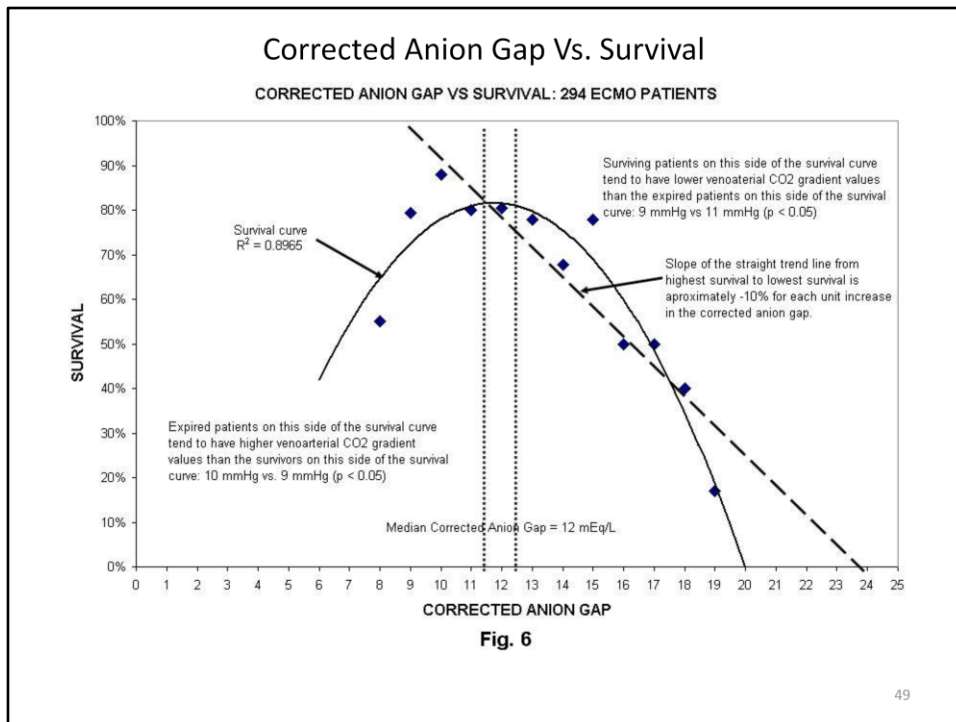
Fig. 6

The average AGc value correlated to survival for each of 294 ECMO patients with a variety of diagnoses while on ECMO.

This figure illustrates the average AGc value correlated to survival for each of 294 ECMO patients with a variety of diagnoses while on ECMO. The maximum survival rate of about 90% occurs when the AGc is 10 mEq/L. As the AGc increases survival decreases. Patients with average AGc values of 20 mEq/L or greater have 90% mortality. The slope of this drop from 10 to 20 mEq/L is about -10%, indicating that an increase of 1 mEq/L in the AGc results in a decrease of survival by about 10%.

However an interesting observation occurs with the line of best fit. This line is parabolic in shape with the maximum survival occurring at 10 mEq/L at the top of the curve and survival falling off on either side as the AGc decreases or increases. While it is expected that mortality would increase as the AGc increases, it is surprising to find that mortality increases as the AGc decreases below 10 mEq/L. The AGc is a reflection of changes in intracellular pH due to the accumulation of organic acids in the anoxic lethal corner cells. But if a patient with a low AGc expires it does not mean that the intracellular pH was not low. It simply means that intracellular pH was changed by a mechanism other than the accumulation of organic acid hydronium cations within the cells. In other words, there is a second mechanism besides poor oxygenation that changes intracellular pH.

Arterial Blood Gas Interpretation

ACIDOSIS

Respiratory acidosis w/ renal compensation

Base > + 2.2 mEq/L

pCO2 > 45 mmHg → Base -2.4 to + 2.2 mEq/L → Respiratory acidosis

Base < - 2.4 mEq/L

Mixed respiratory and metabolic acidosis

pH < 7.40 → pCO2 34-45 mmHg

Base < - 2.4 mEq/L

Metabolic acidosis

pCO2 < 34 mmHg

Base < - 2.4 mEq/L

Metabolic acidosis w/ respiratory compensation

ALKALOSIS

Mixed respiratory and metabolic alkalosis

Base > + 2.2 mEq/L

pCO2 < 34 mmHg → Base -2.4 to + 2.2 mEq/L → Respiratory alkalosis

Base < - 2.4 mEq/L

Respiratory alkalosis w/ renal compensation

pH > 7.40 → pCO2 34-45 mmHg

Base > + 2.2 mEq/L

Metabolic alkalosis

pCO2 > 45 mmHg

Base > + 2.2 mEq/L

Metabolic alkalosis w/ respiratory compensation

50

The usual interpretation of the arterial blood gas follows a pattern like that shown above. First the paH is evaluated, then the paCO2. The determination is made if the acidosis or alkalosis is respiratory or metabolic, which are often modified by compensation mechanisms. The problem for perfusionists and their patients is that this only works for a patient breathing under his own power. Once a patient is placed on a positive pressure ventilator or mechanical cardiopulmonary support, the traditional mode of ABG interpretation is useless because the ventilator or the pump do not allow the patient's physiology to compensate naturally. In fact, the accepted ABG interpretation under these conditions is worse than useless because it can lead to false reassurance that the patient is stable and has a survivable physiology. The ABG of a patient on a ventilator or extracorporeal support does not provide a reliable measure of tissue pH or pCO2. The only reliable parameter that an ABG provides is the paO2 which reflects the lungs' ability to exchange oxygen based on changes in the ventilator FiO2. In univentricular patients with mixed systemic and pulmonary blood flow, even this measurement is unreliable.

Arterial blood gas interpretation is the worst dogma in all of critical care and perfusion practice. Without an accompanying central venous blood gas, the ABG cannot be relied upon to assess a patient's physiology. The APACHE III score relies on both the arterial pH and the arterial pCO2 to determine one of the score's most important factors. A paH of 7.40 and a pCO2 of 40 mmHg would not add any points to the mortality score. However, a venous blood gas drawn on the same patient at the same time with a pvH of 7.00 and a pvCO2 of 80 mmHg would indicate that the patient is on the verge of imminent death, but not because of the abnormal pH or pCO2. Rather it is the gradient of 40 mmHg between the paCO2 and the pvCO2 which indicates a lethal level of tissue CO2 which will quickly lead to organ dysfunction, hemodynamic instability and cardiac failure and arrest.

Shock Induced Intracellular Hypercapnea in Various Organs*			
Species	Organ	Intracellular pCO2 mmHg Before Shock	Intracellular pCO2 mmHg After Shock
dog	muscle	31	53
dog	muscle	51	65
pig	stomach	33	53
rabbit	small gut	25	99
human	brain	58	80
rat	brain	49	149
rat	brain	80	389
dog	kidney	41	102
dog	kidney	42	122
dog	kidney	60	320
human	heart	65	182
dog	heart	33	248
pig	heart	61	359
dog	heart	66	416
	Range	25-80	53-416
	Average	50 +/- 16	188 +/- 132

*Data from Johnson and Weil, 1991.

The Hypercapnic Lethal Corner

51
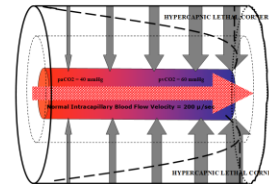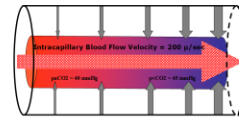
The effect of shock and ischemia on the intracellular pCO2 of various organs. Data complied from Johnson and Weil, 1991.

A meta-analysis published by Johnson and Weil demonstrates the effect of shock on intracellular pCO2. Shock was initiated by hypoxia, reduced blood flow or absolute ischemia in the various experiments. The baseline tissue pCO2 averaged 50 mmHg, followed by a 3.6 fold increase to 188 mmHg during shock. The pCO2 increase is smaller in non-essential muscles, stomach and gut. But in essential organs such as the brain, kidneys and heart, the intracellular pCO2 increase can be enormous. These experiments give some idea about the magnitude to which the intracellular CO2 concentration can rise during shock. However this kind of direct assessment of intracellular pCO2 in the clinical setting is impractical. If tissue pCO2 measurements could be made directly on specific organs such as the brain or heart, these would only reflect a local or regional effect. The only practical method to assess intracellular pCO2 is to measure the venoarterial CO2 gradient as suggested by the Krogh model.

The Venoarterial Carbon Dioxide Gradient
[p[v-a]CO2]

- Normal p[v-a]CO2 = 7 mmHg
- Example 1: Respiratory acidosis vs CO2 breakthrough
  - ABG: 7.31 / 48 / 375 (pH / pCO2 / pO2)
  - VBG: 6.90 / 106 / 26 (pH / pCO2 / pO2)
    - p[v-a]CO2 = 58 mmHg
    - CI = 18 ÷ p[v-a]CO2 = 0.31 L/min/M^2
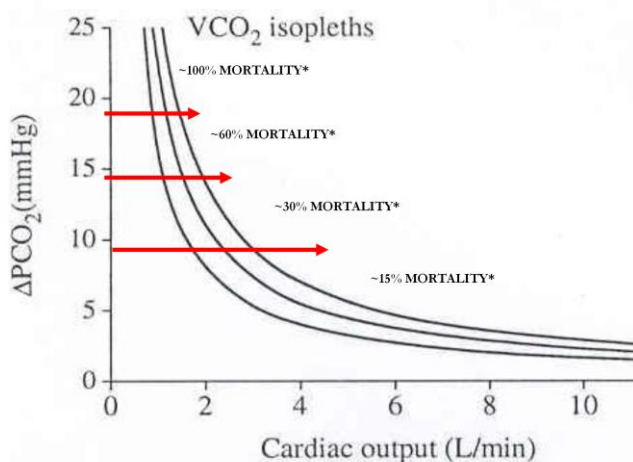- Example 2: Respiratory alkalosis prior to CO2 breakthrough
  - ABG: 7.35 / 32 / 154 (pH / pCO2 / pO2)
  - VBG: 7.29 / 57 / 37 (pH / pCO2 / pO2)
    - p[v-a]CO2 = 25 mmHg
    - CI = 18 ÷ p[v-a]CO2 = 0.72 L/min/M^2

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The magnitude of the accumulation of CO2 within the tissues can be masked in the patient unless both arterial and venous blood gases are measured at the same time. In a real life example, an arterial blood gas, 7.31 / 48 / 375 (pH / pCO2 / pO2), is diagnosed as a mild respiratory acidosis. This interpretation would normally prompt an increase in the ventilator rate and/or airway pressure which tends to impair cardiac function. A venous blood gas drawn at the same time was 6.90 / 106 / 26. The venoarterial CO2 gradient was shown to be a colossal 58 mmHg. An elevated venoarterial CO2 gradient is associated with sub-optimal cardiac function and poor perfused capillary density. Increasing the ventilator rate or airway pressure in an ill conceived attempt to reduce the paCO2 would further impair cardiac function and hasten this patient's demise. This particular patient died from a large brain hemorrhage within 24 hours of being placed on ECMO. Contrary to the interpretation from the arterial blood gas, this patient did not have respiratory acidosis in the true sense that CO2 was being retained at the pulmonary level. In fact, the lungs were working extremely well to reduce the pCO2 from 106 to 48 mmHg and to increase the pO2 from 27 to 375 mmHg. What was diagnosed as arterial hypercapnea was in reality 'CO2 breakthrough' to the arterial blood due to the overwhelming inflow of CO2 into the lungs by the venous blood. This indicates severe cardiac dysfunction and poor perfused capillary density resulting in a lethal intracellular acidosis caused by CO2 accumulating in the tissues.

A second example illustrates how the arterial blood gas may appear hypocapnic while the venous blood gas is hypercapnic simultaneously. The arterial blood gas is 7.35 / 32 / 154 which can be interpreted as a mild metabolic acidosis with respiratory compensation. However, the venous blood gas is 7.29 / 57 / 37. There is no 'CO2 breakthrough' yet, even though the venous CO2 is elevated. But the venoarterial CO2 gradient is 25 mmHg, much higher than the normal 7 mmHg. So if only the arterial blood gases were examined, there would be no laboratory confirmation that the patient's cardiac function is sub-optimal and that tissue acidosis is critical. This patient also died of a large brain hemorrhage.

According to the Krogh model, the venoarterial CO2 gradient can be used to assess the global degree of intracellular trapping of CO2. The mortality rate will increase as the venoarterial CO2 gradient increases until a point is reached beyond which no patient can survive.

Venoarterial CO2 Gradient And Survival During Extended Extracorporeal Support

VCO$_2$ isopleths

~100% MORTALITY*
~60% MORTALITY*
~30% MORTALITY*
~15% MORTALITY*

ΔPCO$_2$(mmHg)

Cardiac output (L/min)

Lamia. 2006

* CMH survival to discharge vs. average CO2 gradient on ECMO: n = 454, p < 0.05

A p[v-a]CO2 increase is related to the reduction in cardiac output. This suggests a state of shock in the form of poor capillary perfusion, whatever the cause. Because capillary transit time slows down as the cardiac output declines, there is a larger than normal accumulation of CO2 per unit of venous blood. The capillaries are further overloaded as perfused capillary density declines. This results in fewer open capillaries to remove CO2 from the tissues. These factors generate hypercapnea in the venous blood. The relationship is not linear because a change of cardiac output will result in the greatest increase in p[v-a]CO2 (aka DPCO2) in the lowest range of cardiac output. However a simple formula can be used clinically to estimate the cardiac index. In adults the formula is: Cardiac Index = 12.9 ÷ p[v-a]CO2. In infants the formula is: Cardiac Index = 18 ÷ p[v-a]CO2. Infants use a larger constant because of their greater production of CO2/kg.

This figure illustrates the lethality of a larger than normal p[v-a]CO2 in 454 ECMO patients. Those patients with an average p[v-a]CO2 over time of less than 10 mmHg have the lowest mortality rate (15%). The mortality rate progressively increases until the average p[v-a]CO2 exceeds 20 mmHg correlating to 100% lethality. Even though these patients are being supported by cardiopulmonary bypass in the form of ECMO, the accumulation of CO2 in the tissues causes lethal complications often independent of the primary diagnosis. For example, a patient with a large p[v-a]CO2 who is suffering from pulmonary hypertension may have an intracranial hemorrhage, renal failure, multiple organ failure or just simply failure to improve.

The Venoarterial CO2 Gradient And Weaning From Mechanical Support: Survivor

ECMO BLOOD FLOW VS. CO2 GRADIENT
S/P CAVC, FAIL TO WEAN FROM CPB
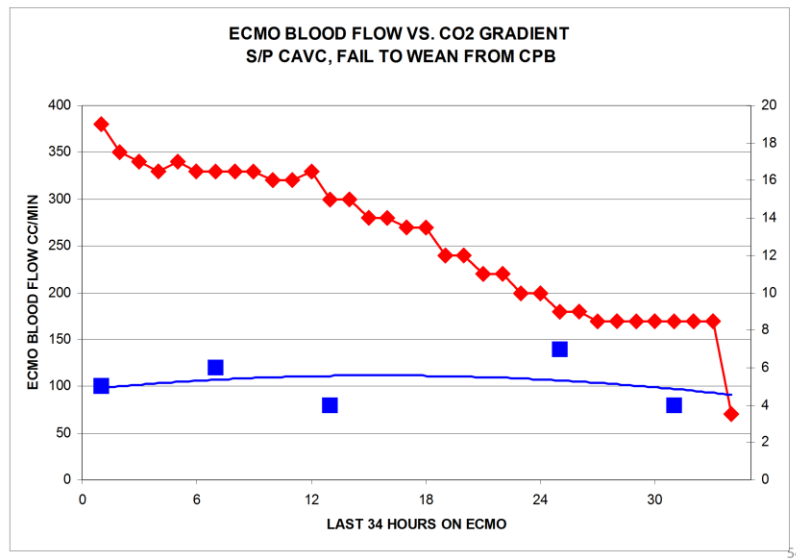
The venoarterial CO2 gradient is the most reliable indicator of a patient's ability to wean from extracorporeal support (IABP, VAD, CPB or ECMO). As an example, a patient was placed on ECMO after failing to wean from CPB. After allowing the heart to recover on ECMO for several days, the ECMO blood flow is weaned over 30 hours as illustrated in the case above. During that time, the venoarterial CO2 remained below 10 mmHg. As the ECMO flow was slowed, the patient's own cardiac output increased, preventing the CO2 gradient from increasing. This indicates survivability off mechanical support.

The Venoarterial CO2 Gradient And Weaning From Mechanical Support: Expired
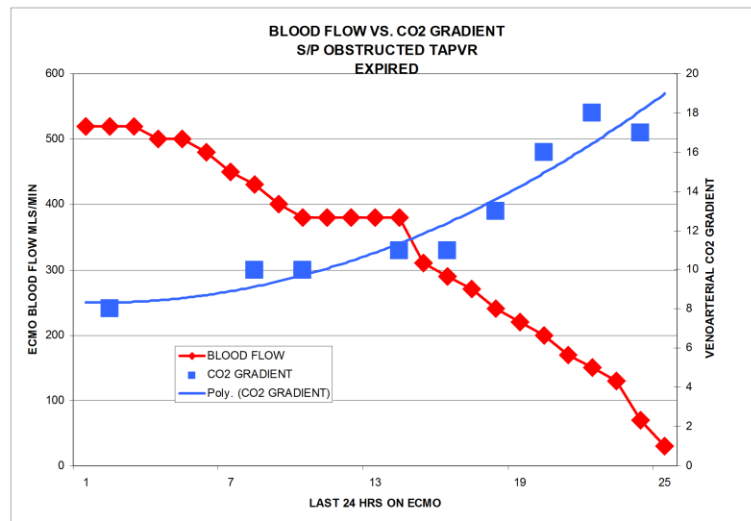
In this example, a patient was also placed on ECMO after failing to wean from CPB. After allowing the heart to recover on ECMO for several days, the ECMO blood flow was weaned over 25 hours as illustrated in the case above. During that time, the venoarterial CO_2 increased above 10 mmHg and continued to worsen as the blood flow was progressively decreased. As the ECMO flow was slowed, the patient's own cardiac output failed to increase, causing the CO_2 gradient to increase. This indicates the inability to survive off mechanical support.

Fig. 7
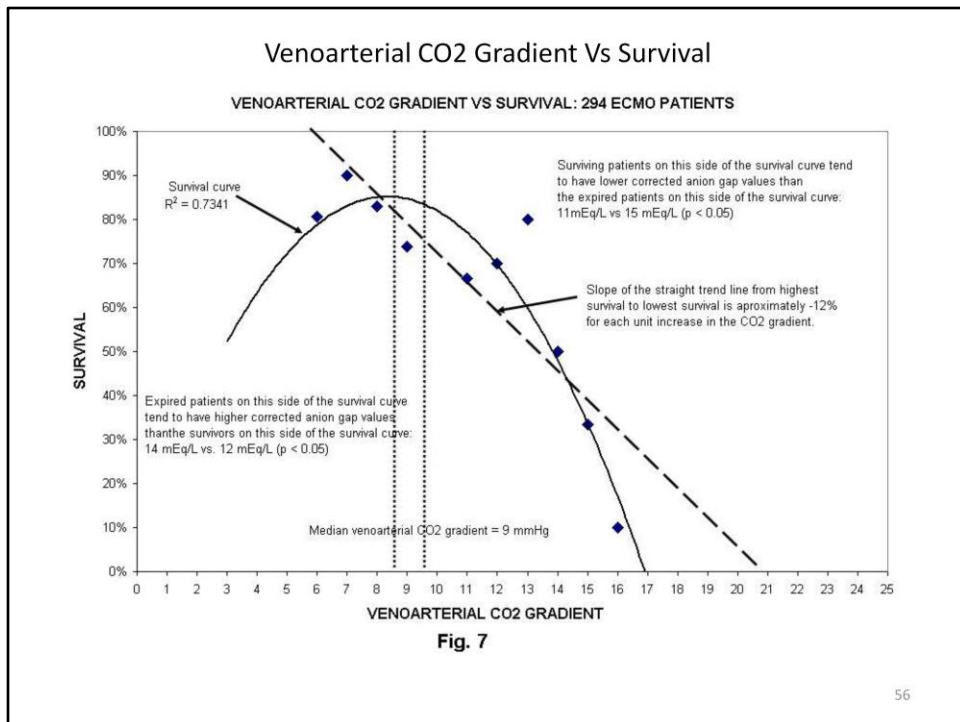
The average venoarterial CO2 gradient correlated to survival for each of 294 ECMO patients with a variety of diagnoses while on ECMO.

This figure illustrates the average p[v-a]CO2 value correlated to survival for each of 294 patients while on ECMO. The maximum survival rate of about 90% occurs when the gradient is about 7 mmHg. As the gradient increases survival decreases. Patients with an average gradient value of 15 mmHg or greater have 90% mortality. The slope of this drop from 7 to 15 mmHg is approximately -12%, indicating that an increase of 1 mmHg in the venoarterial carbon dioxide gradient results in a decrease of survival by about 12%. Like the AGc curve, the line of best fit is parabolic with the maximum survival occurring at 7 mmHg and survival falling off on either side.

Survival Curves Comparison
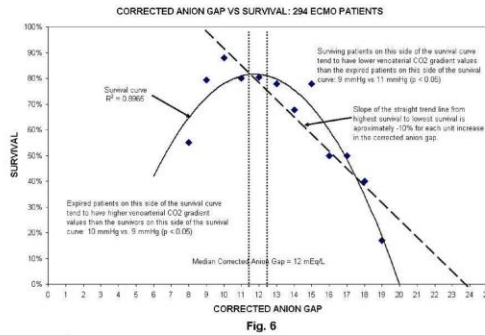
Fig. 6
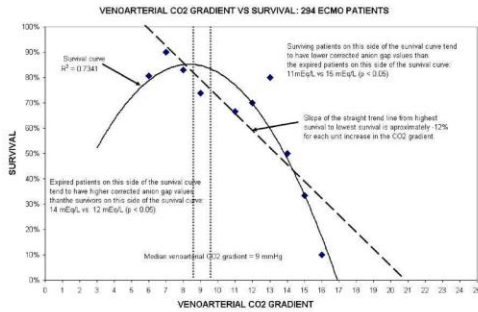
Fig. 7

The curve and slope of the AGc and the curve and slope of the venoarterial CO2 gradient are similar. The effect that each has on survival is similar as well. Expired patients with low venoarterial CO2 gradients had high AGc values and expired patients with low AGc values had high venoarterial CO2 gradients. This explains the parabolic shape of the line of best fit in each graph.

The survival slopes for the anion gap and venoarterial carbon dioxide gradient are about the same (-10 vs.-12). So an increase or decrease of one unit by either parameter has a similar impact on survival. If both the AGc and the venoarterial CO2 gradient are high, survival should be the worst. If both parameters are low, survival should be the best. If one value is high its effect might be balanced by maintaining the other parameter in a low range.

Since the AGc and venoarterial CO2 gradient have a similar impact on survival, a 'Viability Index (VI)' can be calculated simply by adding the values of the parameters together. Viability is the capability of living normally. Theoretically patients with an elevated VI should have an increased morbidity and mortality. Patients with a low VI should have a low morbidity and low mortality.
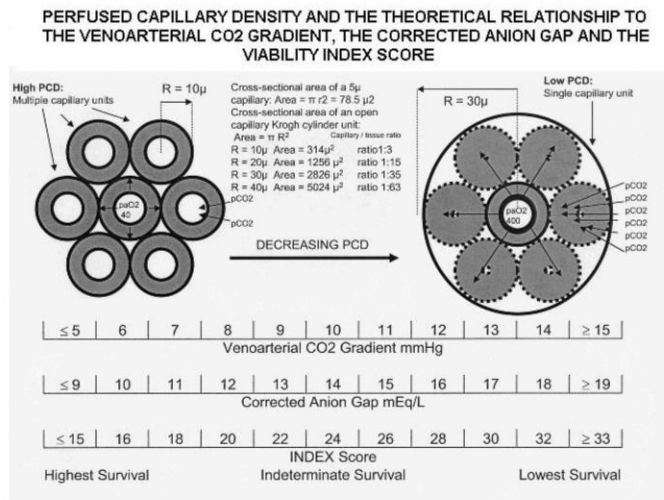
The Viability Index Score

PERFUSED CAPILLARY DENSITY AND THE THEORETICAL RELATIONSHIP TO THE VENOARTERIAL CO2 GRADIENT, THE CORRECTED ANION GAP AND THE VIABILITY INDEX SCORE

Fig. 8

The theoretical relationship between perfused capillary density (PCD), the venoarterial CO2 gradient, the corrected anion gap and the Viability Index Score.

Survival is dependent on maintaining adequate PCD within vital tissues and organs. As long as PCD remains high, the ability to exchange oxygen and carbon dioxide at the microvascular level remains adequate even if the factors governing the Fick principle are sub-optimal. However a patient with a low PCD is at high risk of mortality even if oxygen delivery and hemodynamics are within the normal range. This figure illustrates the theoretical relationship between PCD, the AGc, the p[v-a]CO2 and the Viability Index. Each of the components of the Viability Index (the AGc and the p[v-a]CO2) is an important assessment tool by itself. By combining the components together to create a VI score the assessment value improves. For example, a p[v-a]CO2 of 6 mmHg and a AGc of 10 mEq/L each predict high survival and theoretical correlation to high PCD. A p[v-a]CO2 of 14 mmHg and a AGc of 18 mEq/L each predict poor survival and a theoretical correlation to low PCD.

But what assessment can be made if the p[v-a]CO2 is 6 mmHg and the AGc is 18 mEq/L? The resultant VI score of 24 would indicate an indeterminate survival of only about 50% and the need for more effective intervention. What assessment can be made if the p[v-a]CO2 is 14 mmHg and the AGc is 10 mEq/L ? Again the resultant VI score of 24 would indicate that more effective treatment is necessary.
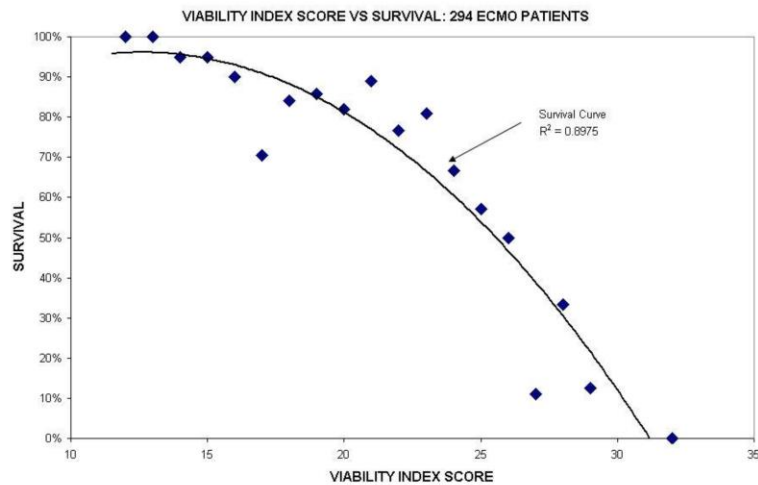
ECMO, The Viability Index Score And Survival

VIABILITY INDEX SCORE VS SURVIVAL: 294 ECMO PATIENTS

Fig. 9

The average Viability Index Score of the 294 ECMO patients calculated from the average AGc and the average venoarterial CO2 gradient.

This figure illustrates the Viability Index survival curve of the same 294 ECMO patients. Patients with scores of 16 or less had greater than 90% survival and patients with scores of 32 or greater had less than 10% survival. Between the scores of 16 and 32 is an indeterminate area of progressively increasing risk of dying.

The line of best fit for the VI survival curve is not parabolic in shape. This probably indicates there is not a prominent third physiologic mechanism besides the two already described herein (an anoxic lethal corner and a hypercapnic lethal corner) that is responsible for a lethal intracellular pH change.

11 Y/O Myocarditis And Cardiogenic Shock: Countdown To Cardiac Arrest

TIME	TYPE	pH	pCO2	pO2	BE	CO2 gradient	Anion Gap	Alb	BUN	Lactic Acid	INDEX
1325							8	2	14	8.6	
1450	ABG	7.38	24	127	-9.4	27					
	VBG	7.19	51	34	-9.3						
1630	ABG	7.41	25	151	-7.1	16					32
	VBG	7.27	41	35	-7.9						
2000	ABG	7.34	25	135	-10.6	15					
	VBG	7.22	40	43	-11						
2216							8		15	9.1	
2350	ABG	7.26	29	128	-13.4	20					34
	VBG	7.14	49	42	-12.7						
0215	ABG	7.21	21	142	-18.2	21					
	VBG	7.09	42	45	-17						
0340	ABG	7.17	27	113	-17.8	20	11	1.5	16	13.3	37
	VBG	7.02	47	36	-18.5						
0500	CARDIAC ARREST										
0527	EXPIRED										

RESUSCITATION INCLUDED:

EPI: 1 MCG/KG/MIN

NOREPI: 0.2 MCG/KG/MIN

VASOPRESSIN: 4 MU/KG/MIN

13 L CRYSTALLOID

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This case is an example of how the Viability Index score would have benefited a patient if it had been utilized. A patient with myocarditis was resuscitated using increasing doses of inotropes, vasopressors and fluid for volume expansion. In the first 6.5 hours, the VI score was 32, at the very bottom of the survival curve. This score alone would not necessarily suggest the need for mechanical cardiopulmonary support if the resuscitation efforts had succeeded. However over the next 7.5 hours the failure of the resuscitation was apparent as the VI score continued to increase. Over the next 2 hours the VI score increased yet again, suggesting the immediate need to implement extracorporeal support. However this was not forth coming. The patient finally arrested and could not be revived after 27 minutes of CPR with ACLS.

If the patient had been placed on extracorporeal support after 2000, the further worsening of the VI score and the cardiac arrest could have been avoided. The patient may or may not have succumbed at a later date to his myocarditis even with ECMO support, but that opportunity to survive was not realized. In addition, placing the patient on ECMO too late at 0340 or even 2350 would have exposed him to the ravages of reperfusion injury aggravated by the pump, further reducing chances for survival.

Timing is an important aspect of implementing extracorporeal support; 'the earlier the better' is thought to offer the best chance of survival. However outside of the Viability Index there is no quantifiable standard to determine if extracorporeal support is early enough or too late to save the patient.

Viability Index Cut Points And Survival

ECMO PATIENTS: SURVIVAL BELOW AND ABOVE THE CUT-POINTS (FISHER'S EXACT TEST)			
	1ST AGc < 23 mEq/L	1ST AGc ≥ 23 mEq/L	TOTAL
SURVIVORS	169 (80%)	3 (1%)	172 (82%)
EXPIRED	32 (15%)	6 (3%)	38 (18%)
TOTAL	201 (96%)	9 (4%)	210 (100%)
p = 0.0014			
	1ST p(v-a)CO2 < 16 mmHg	1ST p(v-a)CO2 ≥ 16 mmHg	TOTAL
SURVIVORS	170 (81%)	2 (1%)	172 (82%)
EXPIRED	33 (16%)	5 (2%)	38 (18%)
TOTAL	203 (97%)	7 (3%)	210 (100%)
p = 0.0024			
	1ST VI < 28	1ST ≥ 28	TOTAL
SURVIVORS	163 (78%)	9 (4%)	172 (82%)
EXPIRED	26 (12%)	12 (6%)	38 (18%)
TOTAL	189 (90%)	21 (10%)	210 (100%)
p = 0.0001			

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The survival of ECMO patients is correlated to the average AGc and the average p[v-a]CO2 during the ECMO run. A related method looks at the very <u>first</u> AGc and p[v-a]CO2 just before or just after the beginning of ECMO. At the micro-vascular tissue level, the AGc detects tissue anoxia and the p[v-a]CO2 detects tissue carbon dioxide retention, both of which are caused by poor perfused capillary density. Together, these risk markers detect tissues with localized hypoxic ischemia which is caused by various types and degrees of shock.

The first AGc beyond 22 mEq/L or the first p[v-a]CO2 beyond 15 mmHg (both of these are cut points) predict certain patients as being high risk as illustrated in the table above. Unfortunately the first AGc by itself only identifies 9 (4%) of the 210 ECMO patients as high risk and the first p[v-a]CO2 by itself only identifies 7 (3%) of the 210 ECMO patients as high risk. Generally any AGc elevated above the highest normal value (>14 mEq/L) usually indicates that the tissues are experiencing some degree of hypoxia. Any p[v-a]CO2 above the highest normal value (>7 mmHg) indicates that the tissues are experiencing some degree of carbon dioxide retention. Moderately elevated AGc values or moderately elevated p[v-a]CO2 values by themselves are not necessarily lethal. The cells can tolerate one or the other up to a certain cut point; < 16 mmHg for the p[v-a]CO2 and < 23 mEq/L for the AGc.

In contrast, the first Viability Index identifies 21 (10%) of the 210 ECMO patients as high risk, two to three times more than the first AGc alone or the first p[v-a]CO2 alone. If both the AGc and the p[v-a]CO2 are moderately elevated at the same time (even to levels less than the cut points), cells are less capable of tolerating the dual effects of hypoxia and carbon dioxide retention simultaneously. These effects are apparently cumulative which explains the need to monitor the Viability Index. The Viability Index measures the extent of this dual effect; reaching its lethal tipping point at 28.

SHOCK AND ECMO PATIENT SURVIVAL
(N = 284)
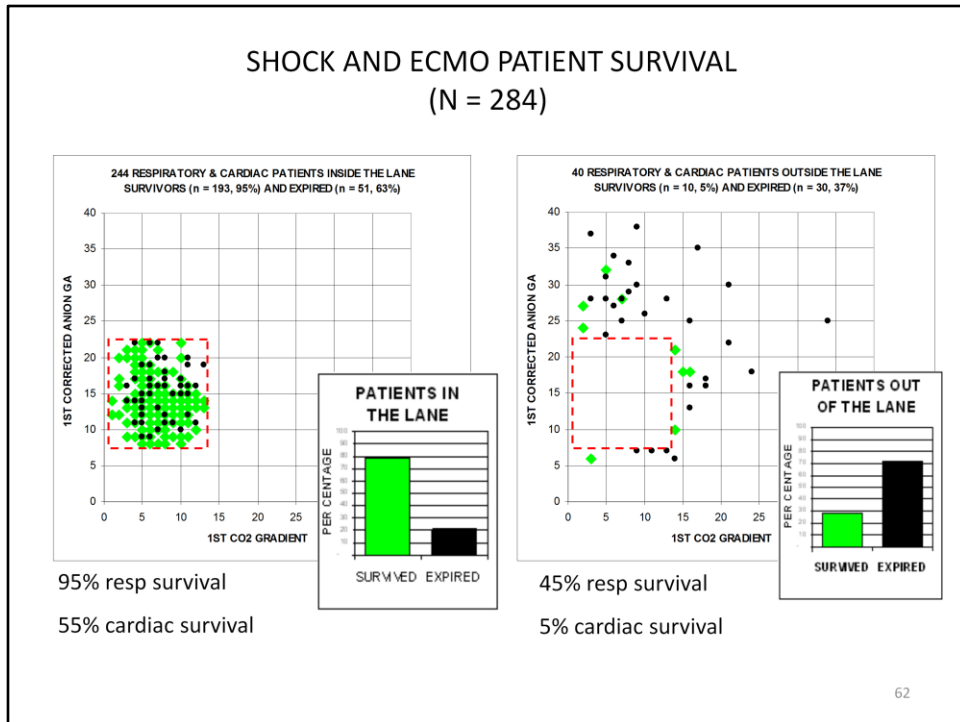
The level of shock that a patient is enduring can be determined using the Viability Index (VI) with high scores correlating to a high level of shock. These charts contain the first VI score just before or just after patients were placed on ECMO. The patient population was pediatric with most patients weighing less than 10 kg. The diagnoses varied in two broad categories; respiratory and cardiac. The respiratory diagnoses included all the traditional neonatal ECMO conditions (with the exception of congenital diaphragmatic hernia); meconium aspiration, primary pulmonary hypertension, respiratory distress syndrome and sepsis. In older patients, diagnoses included primarily pneumonia, respiratory syncytial virus, sepsis and trauma. The most common cardiac diagnoses included pre and post surgery for congenital heart disease and myocarditis or cardiomyopathy.

The VI scores of 95% of the survivors fall into a relatively small area between the corrected anion gaps of 7 and 22 mEq/L and the venoarterial CO_2 gradients of 1 and 13 mmHg. This small area is known as the "lane" in reference to the rectangular area beneath a basketball goal from which a player is most likely to make a goal. Only 61% of the expired patients are located in the lane. The mortality for patients in the lane is 21%.

By contrast, only 5% of the survivors are located outside the lane along with 39% of the expired patients. The patients outside the lane have a mortality rate of 73%, 3.5 times higher than for patients in the lane.

Why such a difference? Patients outside the lane are at a higher level of shock than patients in the lane. Because the Viability Index score relates to the inadequacy of perfusion, the most likely cause for the increased mortality outside of the lane are complications from reperfusion injury caused by the sudden reperfusion of hypoxic ischemic tissues by the ECMO pump. This can manifest itself in many ways; brain hemorrhage or infarct, pulmonary hemorrhage, cardiac stun, renal failure, multiple organ failure or simply failure to improve from a known reversible condition. Rarely does the patient die of the original diagnosis of cardiac failure or pulmonary failure.
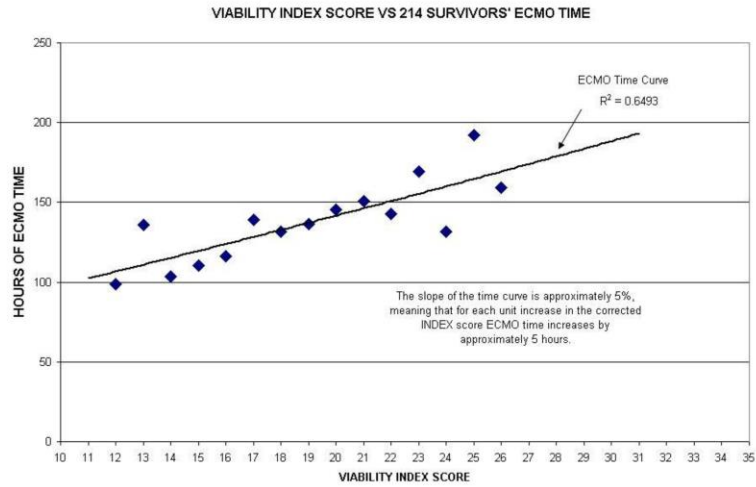
ECMO Time And The Viability Index

VIABILITY INDEX SCORE VS 214 SURVIVORS' ECMO TIME

Fig. 10

The ECMO time increases with higher Viability Index Scores.

Theoretically the VI is a reflection of the status of the intracellular pH milieu; the higher the score the greater the disruption of intracellular physiology. So more time is needed to normalize homeostasis. This theory is supported by the fact that patients with an elevated VI who survive tend to be on ECMO for longer periods.

The Viability Index Score: Summary

- Initial VI scores assess viability potential & risk of reperfusion injury:
  - </= 16: good viability, low reperfusion injury risk
  - 16>32: progressively decreasing viability and increasing risk of reperfusion injury
  - =/> 32: poor viability, high reperfusion injury risk

- Subsequent VI scores assess improving or worsening viability potential:
  - Falling VI indicates improving viability
  - Increasing VI indicates worsening viability

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A Viability Index (VI) score taken prior to intervention can predict the survival potential in patients with reversible conditions. For example, if a patient's VI score is 16 or less prior to initiation of ECMO the risk of dying is less than 10%. By contrast, if the VI score is 32 or greater the risk of dying is 90%. Subsequent VI scores indicate if the patient is improving (resolution of shock) or worsening. If a lethal anatomic lesion is present, such as irreparable congenital heart disease or fibrotic lung disease, maintenance of the VI in a survivable range will be of no benefit in terms of reversing the disease. However maintaining such a patient in a survivable VI range may reduce any morbidity that would rule the patient out as a possible transplant candidate.

Viability Index Cut Point and Survival: Three Examples

DAILY VIABILITY INDEX VALUES AND SURVIVAL: THREE PATIENT EXAMPLES
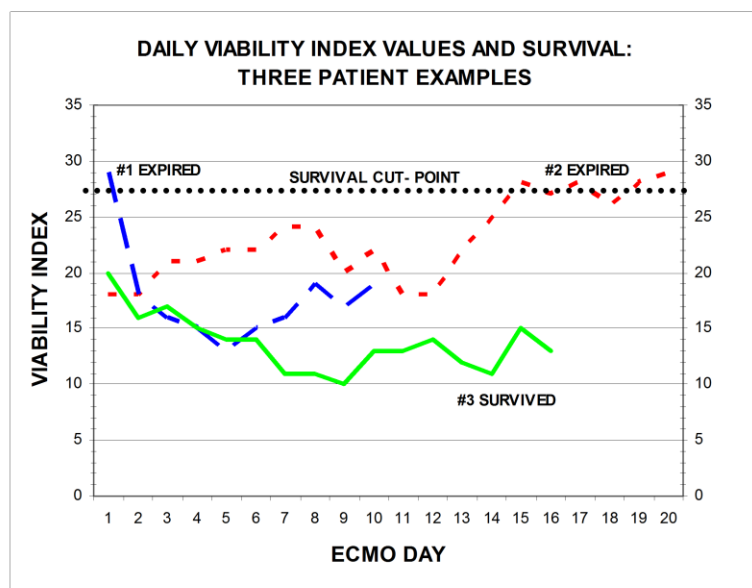
By systematically assessing the Viability Index (VI) over a period of time, the effectiveness of interventional support can be determined by the direction that the VI moves within the indeterminate area of the VI survival curve. For example, if the first VI on day 1 of ECMO is 24 but falls to 20 by the second day, this indicates that the intervention is effective. On the other hand, if the VI increases from 24 to 28, the intervention is not working and the patient will probably expire without a change in strategy. If a patient is placed on ECMO and develops a VI that exceeds the survival cut point, a fatal reperfusion injury may ensue even if prior or subsequent VI values are within a survivable range. In this figure are three examples of the daily Viability Index and survival.

Patient #1 (long dash line) had a moderate survival diagnosis (pulmonary hypertension: expected survival = 75%), but the VI on the first ECMO day exceeded the hypothetical survival cut point (dotted line). The remaining days on ECMO were all below the cut point. Patient died of a large brain infarct that was detected by head ultrasound on ECMO Day 10. This complication probably occurred on the first day as a result of reperfusion injury. Even though subsequent VI scores were in the normal range, the brain damage caused by reperfusion injury on the first day resulted in the patient's demise.

Patient #2 (short dash line) had a low survival diagnosis (Pertussis: expected survival = 30%). The VI remained below the survival cut point for the first 14 ECMO days, but then rose above the cut point during the final week on ECMO. Patient died of multi-system organ failure, the pulmonary disease never having improved.

Patient #3 (solid line) had a moderate survival diagnosis (sepsis: expected survival = 75%). The VI during ECMO never exceeded the hypothetical survival cut point, so the patient was not at risk for lethal reperfusion injury. Patient survived without complications.
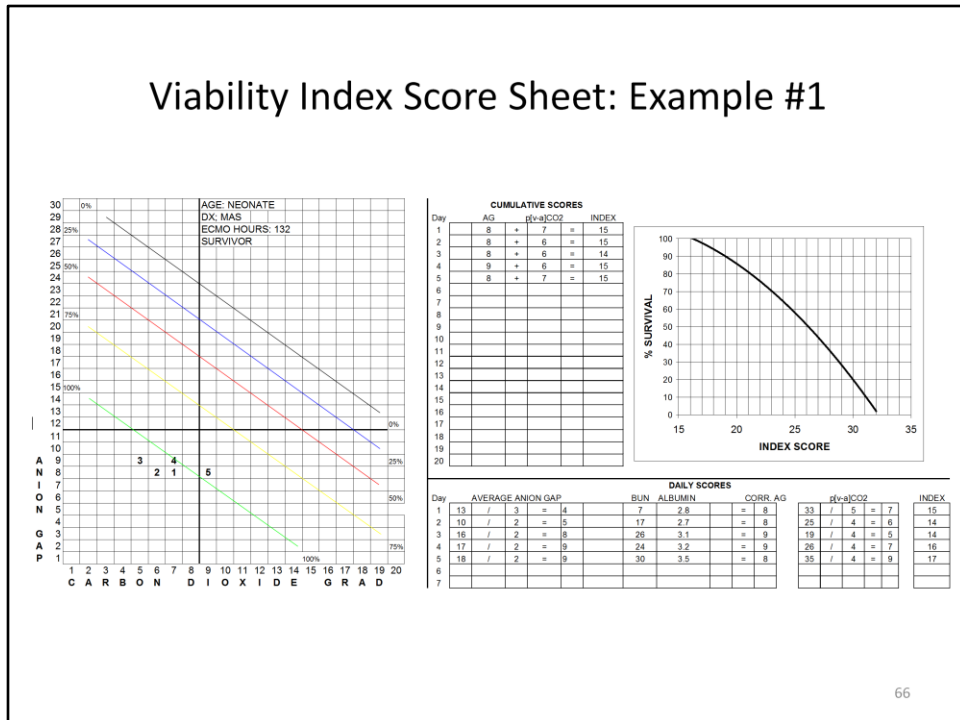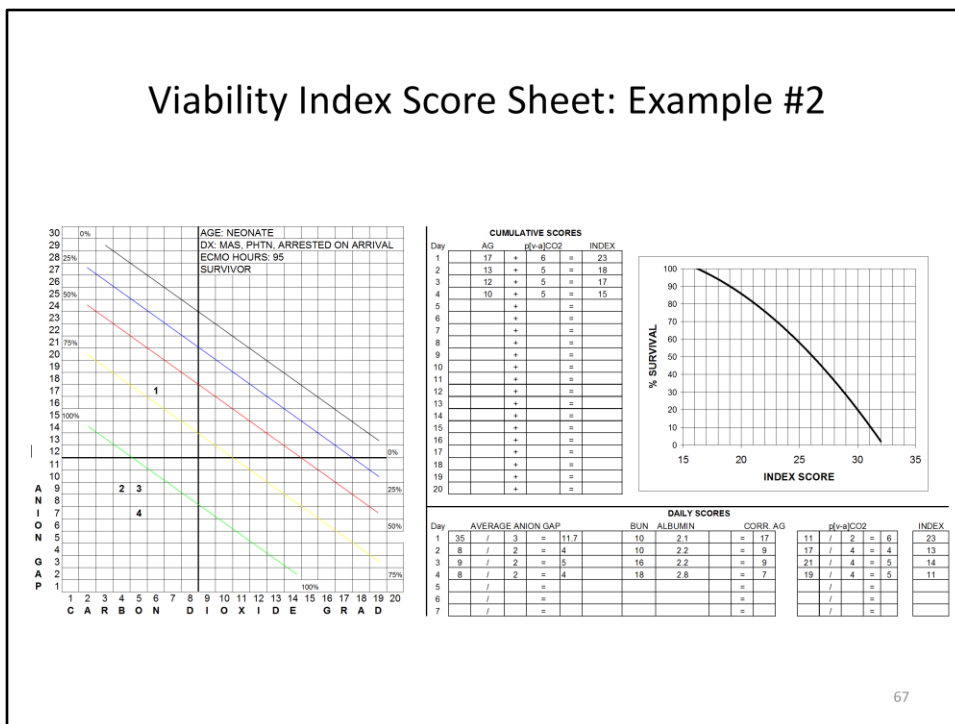
Example 1. Score sheet illustrating the progression of the daily Viability Index Score and the Cumulative (average) Viability Index Score. The VIS and CVIS are low due to early intervention. The patient survived.

A VI score sheet illustrates how the VI can be used to monitor a patient's progress throughout a period of extracorporeal support. In Example 1, under "Daily Scores" the AGc values are averaged. For Day 1, the three uncorrected AG values totaling 13 mEq/L have an average of 4 mEq/L. Correction factors for the BUN and albumin are then used to arrive at the AGc value of 8 mEq/L. The venoarterial CO_2 gradient for Day 1 is calculated by adding the five values together for a total of 33. This is then divided by 5 to obtain the average for the day of 7 mmHg. The AGc and the venoarterial CO_2 gradient for Day 1 are then added together to obtain the Day 1 Daily VI score of 15. This score is then plotted as a "1" on the grid at the left to represent the Day 1 Daily VI score. Subsequent daily scores are plotted ("2,3,4,etc") to make possible the visualization of changes in the patient's intracellular physiology during extracorporeal support.

The diagonal lines in the plot graph represent quartiles of survival; the area around the lowest line having the highest survival and the area around the highest line having the poorest survival. These quartiles are derived from the VI survival curve in the upper right of the score sheet. The curve on this graph is plotted based on the survival of ECMO patients as it relates to the overall VI called the "Cumulative Viability Index Score" (CVIS) of 294 past ECMO patients. The CVIS is the average of the daily VI score averages. The Day 1 CVIS is the same as the Day 1 Daily VI score, but the Day 2 CVIS is the average of the Day 1 Daily VI score and the Day 2 Daily VI score. In this example, the Day 1 CVIS is 15 which is near the highest predicted survival. As long as the CVIS remains high on the survival curve, patient survival with few complications can be expected.
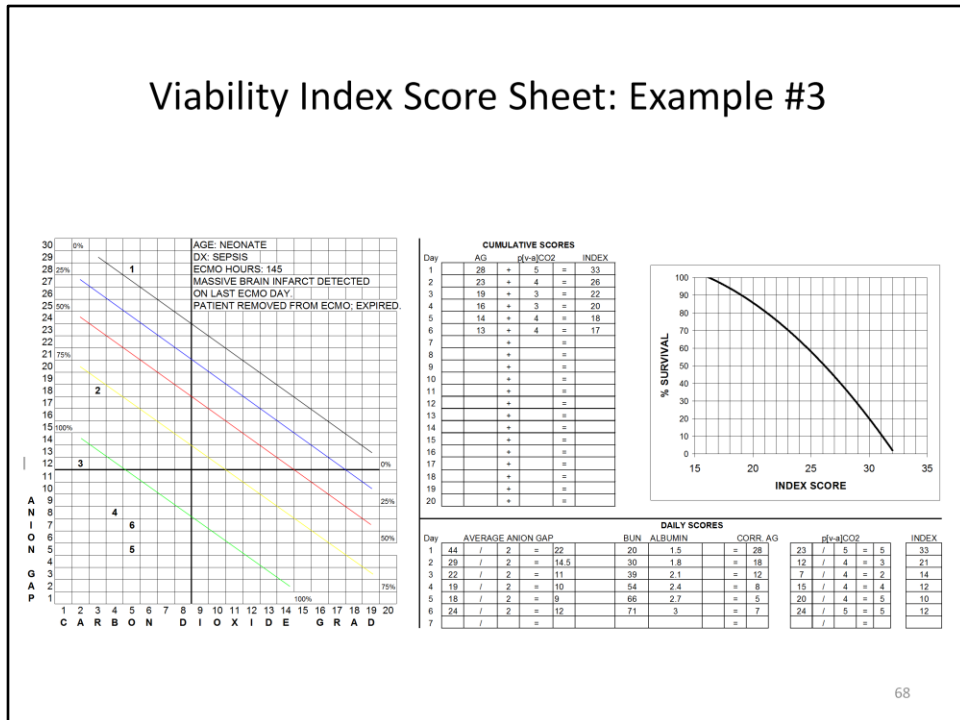
Viability Index Score Sheet: Example #2

Example 2   Viability Index Score sheet illustrating a Day 1 VIS elevation due to pre-ECMO cardiac arrest. The patient survived.

In Example 2, the Day 1 Daily VI score of 23 plots lower on the survival curve than the previous example. This patient arrested just prior to ECMO and the elevated Day 1 Daily VI score is a reflection of the physiologic stress experienced by the patient. However, subsequent daily and cumulative scores demonstrate that the patient recovered from the stress quickly after the initiation of ECMO. As the VI score continued to improve over subsequent days there was an ever decreasing risk of a dangerous complication or death.

Viability Index Score Sheet: Example #3

Example 3   Viability Index Score sheet illustrating a Day 1 VIS elevation beyond the point of no return with sluggish return to normal over a 72 hour period. The patient expired due to brain damage.

In Example 3, the Day1 Daily VI score of 33 plots at the very bottom of the survival curve. The Day 2 Daily VI score improves to only 21, demonstrating relatively sluggish recovery before the day 3,4,5 & 6 daily VI scores fall into an acceptable range. Even though the CVIS eventually falls to 17, the first VI score of 33 on the first ECMO day represents a 'VI point of no return' beyond which most patients will not survive. The 'VI point of no return' seems to be 32 or greater for all patients and probably quantifies the degree of intracellular acidosis resulting in irreversible damage to one or more vital organ systems.

There is probably a temporal component to the point of no return as well. Patients with a high VI for only a few minutes before extracorporeal support will probably have a better chance for survival compared to patients whose vital signs are supported with maximum medical management for hours or days but whose high VI fails to improve. The false reassurance of acceptable vital signs concomitant with a high VI can fatally delay the initiation of extracorporeal support.

The initiation of ECMO was too late to save the patient in Example 3 although the cause of death (a brain infarct) was not readily apparent until 5 days later. Monitoring of the VI before ECMO might have prompted earlier ECMO intervention at a lower VI and a better chance for survival.

Case Reports

Parameter	ECMO Patient # 48	ECMO Patient # 306
Age & wt.	1 day / 4.1 kg	8 mos / 6.4 kg
Dx	TGA w/o VSD, failed Rashkind, failed off CPB septostomy, aggressive resuscitation required prior to ECMO.	Cardiomyopathy, adenovirus, aggressive resuscitation required prior to ECMO.
Pre-ECMO lab values	ABG = 7.14/40/44/-14 VBG = none 'p(v-a)CO2 ? CAG = 28 mEq/L Pre-ECMO INDEX ? ≥ ~ 35	ABG = 6.70/51/42/-28 VBG = 6.34/63/41/-22 'p(v-a)CO2 = 12 mmHg CAG = 24 mEq/L Pre-ECMO INDEX = 36
1st ECMO lab values	ABG = 7.31/48/375/-2 VBG = 6.90/106/26/-8 'p(v-a)CO2 = 58 mmHg CAG = 28 mEq/L INDEX = 86	ABG = 7.35/32/249/-7 VBG = 7.30/39/33/-7 'p(v-a)CO2 = 7 mmHg CAG = 24 mEq/L INDEX = 31
Complications / outcome	Massive ICH @ ECMO hr. 25 Pt. Expired.	L MCA infarct by CT Weaned from ECMO @ 87 hr. Referred for eventual transplant.
Comments	ECMO delayed at least 14 hrs during cath lab procedure and open septostomy.	Pt. Placed on ECMO quickly once resuscitation was required, less than 1 hour delay.

These 2 case reports demonstrate how the Viability Index (VI) can be useful in the acute setting. In case #48, an infant with transposition of the great arteries failed both a balloon atrial septostomy and an off CPB septectomy. The patient required very aggressive resuscitation prior to being placed on ECMO. Just prior to ECMO, an ABG was performed showing a normal paCO2. The corrected anion gap was 28 mEq/L. In hindsight, scoring the patient before the attempted atrial septostomy and septectomy might have indicated the need for ECMO 14 hours earlier. But because of the delay, the first VI score on ECMO was 86, meaning that the patient was going to die of a reperfusion injury complication.

In case #306, a child with cardiomyopathy required very aggressive resuscitation prior to being placed on ECMO. However, there was just a 1 hour delay from the start of resuscitation to implementation of ECMO. The p[v-a]CO2 prior to ECMO indicated adequate resuscitation efforts but poor tissue oxygenation (a high corrected anion gap). Once on ECMO the first Viability Index score was 31. The risk of a reperfusion injury was elevated and manifested itself as a left middle cerebral artery infarct. This was detected after the patient successfully weaned from ECMO and survived to hospital discharge functionally intact.

Summary

- AGc and the p[v-a]CO2 are indirect assessments of intracellular pH within the cells of the lethal corner.

- Viability index scores reveal the degree of survival potential that can be masked by natural or iatrogenic compensation mechanisms used to normalize lab values and vital signs.

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In summary, both the AGc and the p[v-a]CO2 are indirect assessments of intracellular pH within the cells of the lethal corner. The increasing magnitude of either parameter is indicative of a lethal intracellular acidosis that is not necessarily detected by conventional blood gas or electrolyte interpretation.

The Viability Index (VI) can quantify the magnitude of the shock that the patient is experiencing. Internal, iatrogenic or perfusionist directed compensation mechanisms may normalize blood gas values and vital signs without actually improving the lethal intracellular acidosis of the lethal corner. In theory, the greater the VI the larger the lethal corner and the more severe the shock. So understanding the principles of the Oxygen Pressure Field and the VI may help the perfusionist to develop perfusion strategies more likely to result in a favorable outcome.

End of Session 2: References

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1. Grist G. Oxygen Pressure Field Theory: A Detailed Description Of Vital Gas Exchange At The Capillary Level For Perfusionists. Canadian Perfusion Canadienne 2006; 16(2):65-71.
2. Willis N, Mogridge J. Indicators of histohypoxia. Acta Anaesthesiol Scand Suppl 1995; 107:45-8.
3. Madias NE, Homer SM, Johns CA, Cohen JJ. Hypochloremia as a consequence of anion gap metabolic acidosis. J Lab Clin Med 1984; 104(1):15-23.
4. Emmett M, Narins RG. Clinical use of the anion gap. Medicine (Baltimore) 1977; 56(1):38-54.
5. Hertford JA, McKenna JP, Chamovitz BN. Metabolic acidosis with an elevated anion gap. Am Fam Physician 1989; 39(4):159-68.
6. Ishihara K, Szerlip HM. Anion gap acidosis. Semin Nephrol 1998; 18(1):83-97.
7. Paulson WD, Roberts WL, Lurie AA, et al. Wide variation in serum anion gap measurements by chemistry analyzers. Am J Clin Pathol 1998; 110(6):735-42.
8. Figge J, Jabor A, Kazda A, Fencl V. Anion gap and hypoalbuminemia. Crit Care Med 1998; 26(11):1807-10.
9. Roy BJ, Rycus P, Conrad SA, Clark RH. The changing demographics of neonatal extracorporeal membrane oxygenation patients reported to the Extracorporeal Life Support Organization (ELSO) Registry. Pediatrics 2000; 106(6):1334-8.
10. Johnson BA, Weil MH. Redefining ischemia due to circulatory failure as dual defects of oxygen deficits and of carbon dioxide excesses. Crit Care Med 1991; 19(11):1432-8.
11. Hoffman TL, LaManna JC, Pundik S, et al. Early reversal of acidosis and metabolic recovery following ischemia. J Neurosurg 1994; 81(4):567-73.
12. Stefanutti G, Pierro A, Vinardi S, et al. Moderate hypothermia protects against systemic oxidative stress in a rat model of intestinal ischemia and reperfusion injury. Shock 2005; 24(2):159-64.
13. Vinardi S, Pierro A, Parkinson EJ, et al. Hypothermia throughout intestinal ischaemia-reperfusion injury attenuates lung neutrophil infiltration. J Pediatr Surg 2003; 38(1):88-91; discussion 88-91.
14. Fiskum G, Rosenthal RE, Vereczki V, et al. Protection against ischemic brain injury by inhibition of mitochondrial oxidative stress. J Bioenerg Biomembr 2004; 36(4):347-52.
15. Dumont L, Stanley P, Chartrand C. The cardiovascular effects of hypertonic sodium bicarbonate in conscious dogs: underlying mechanisms of action. Can J Physiol Pharmacol 1984; 62(3):314-8.
16. Gudis SM, Mangi S, Feinroth M, et al. Rapid correction of severe lactic acidosis with massive isotonic bicarbonate infusion and simultaneous ultrafiltration. Nephron 1983; 33(1):65-6.
17. Howell JH. Sodium bicarbonate in the perinatal setting--revisited. Clin Perinatol 1987; 14(4):807-16.
18. Mikulaschek A, Henry SM, Donovan R, Scalea TM. Serum lactate is not predicted by anion gap or base excess after trauma resuscitation. J Trauma 1996; 40(2):218-22; discussion 222-4.

Beyond Fick: Discussions On Advanced Perfusion Theory

Session 3: Innovative Solutions To Common Perfusion Challenges Using Oxygen Manipulation

Gary Grist RN CCP

No Disclosures

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SESSION 3 TABLE OF CONTENTS

Objectives

1. Describe six circumstances where manipulation of the oxygenator sweep gas FiO2 is needed.

2. Identify scenarios wherein hyperoxia can be of benefit.

3. Identify scenarios wherein hyperoxia can be detrimental.

Some consider it a fact that use of hyperoxia on cardiopulmonary bypass (CPB) has negative effects on patient outcome by increasing the danger of oxygen toxicity or reperfusion injury. This belief has become a 'sacred cow' among many perfusionists. However the manipulation of oxygen on CPB can be used to the patient's benefit. Hyperoxia can be beneficial in one situation and detrimental in another as can normoxia. It is incumbent upon the perfusionist to understand the need for the manipulation of oxygen concentration and master the techniques needed to provide the patient with the greatest benefit. A 'one size fits all' approach to oxygenation strategy, be it normoxia, hyperoxia, or something in between can rob the patient of the benefits that the free range of oxygen manipulation, from high to low, can provide. Oxygen Pressure Field Theory conceptualizes the manipulation of oxygen concentration such that the perfusionist can understand the mechanics of microvascular gas exchange.

Six Scenarios Involving The Manipulation of Oxygen On CPB

1. Nitrogen entrainment
2. Hemodilution
3. Metabolic acidosis
4. Deep hypothermic circulatory arrest
5. Oxygen toxicity
6. Reperfusion injury

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Six scenarios will be discussed wherein the manipulation of oxygen by the perfusionist can have an impact on patient morbidity: 1. nitrogen entrainment, 2. hemodilution, 3. metabolic acidosis, 4. deep hypothermic circulatory arrest, 5. oxygen toxicity and 6. reperfusion injury.

Scenario # 1: Nitrogen Entrainment: CNS Complications

- **Sources of emboli**
  - **atheroemboli from aortic manipulation**
  - **thromboemboli**
  - **bubbles of air**
    - Raymond et al. 2001
- **CNS complications from CPB**
  - **stroke = 1.5% (CABG) to 10% (valves)**
  - **asymptomatic brain infarct by MRI = 18%**
   - Floyd et al. 2006

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The frequency of central nervous system (CNS) complications in patients after cardiopulmonary bypass (CPB) correlates to the type of surgery. Extended time on CPB increases the risk of emboli as does the actual cardiotomy where the heart chambers are opened to the atmosphere. Even when there is no outward appearance of CNS damage, asymptomatic brain infarctions occur in 18% of all CPB patients.

The emboli can be atherosclerotic, thrombotic or gaseous. The gaseous emboli are the most common and numerous and the only type that the perfusionist can actively modify to reduce their threat.

Scenario # 1: Nitrogen Entrainment
Air bubbles in the venous return line

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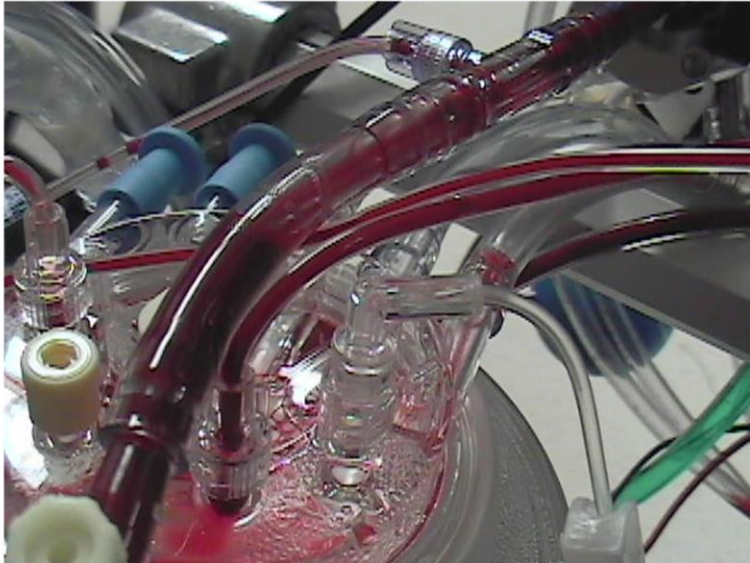
   A common entry way for gaseous emboli is from the venous return line. This picture shows a large air bubble within the venous line as blood is draining into the venous reservoir. Gas bubbles in the venous blood will be primarily room air in composition; meaning about 79% nitrogen and about 21% oxygen. Flooding the operative field with carbon dioxide may help to reduce the nitrogen composition of the entrained bubbles.

Scenario # 1: Nitrogen Entrainment Making bloody meringue

Air emulsification of blood by field suckers and ventricular venting

Another common entry way for gaseous emboli is from the ventricular vent or field sucker pumps. These pumps will often emulsify the air and blood, making a bloody meringue. Meringue is a sweet mixture of egg whites (which are primarily an albumin solution) and sugar beaten at high speed into a thick emulsion as shown in the picture. The emulsion is composed of microscopic air bubbles (mostly nitrogen) encapsulated in an albumin membrane. Because it is an albumin solution, blood can also be emulsified. The albumin membrane keeps the bloody microscopic bubbles intact and makes their removal by buoyancy separation and filtration difficult.

Scenario # 1: Nitrogen Entrainment Perfusionist Interventions
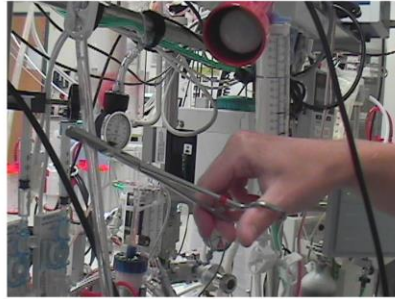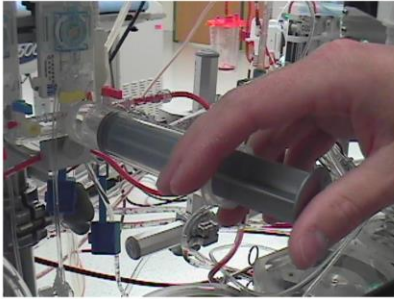
When used, special monitors have detected gaseous microemboli (GME) entering the brain of every patient on CPB. The number of emboli per minute was markedly higher during perfusionist interventions and were associated with the worst patient neuropsychological outcomes.

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Special equipment has detected gaseous microemboli (GME) in the cerebral circulation of all types of patients on CPB who were tested. By extension, the assumption can be made that most, if not all CPB patients are exposed to GME. The GME are most numerous during interventions by perfusionists and were associated with the worst neuropsychological outcomes.

What Do You Do When
The Bubble Detector Starts Ticking ?

THE SPENCER SCALE FOR CLASSIFYING AIR EMBOLI LOAD BY DOPPLER

GRADE	SPENCER CODE	CPB BUBBLE DETECTOR
0	A complete lack of bubble signals.	Does not detect emboli smaller than 40 microns
I	An occasional bubble signal discernable with the cardiac motion signal with the great majority of cardiac periods free of bubbles.	Occasional entry of bubbles > 40 microns
II	Many, but less than half, of the cardiac periods contain bubbles, singly or in groups.	Entry of bubbles > 40 microns every 2-3 seconds
III	Most of the periods contain showers of single-bubble signals, but not dominating or over-riding the cardiac motion signals.	Critical entry of large bubbles
IV	The maximum detectable bubble signal sounding continuously throughout systole and diastole of every cardiac period, and over-riding the amplitude of normal cardiac signals.	Potentially lethal entry of large bubbles

Nishi RY, Brubakk AO, Eftedal OS, Bubble Dectection. In: AO Brubakk; TS Neuman, editors. Bennett and Elliott's Physiology and Medicine of Diving. 5th edn: Saunders; 2003; p. 501-29.

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The Spencer scale was developed by Dr. Merrill P. Spencer MD, PhD (1922-2006) in the 1960's using Doppler devices over the hearts of divers. This scale is quite subjective, but basically, if no bubbles are heard that equals Grade 0. Grade I has a few bubbles. Grade II has more bubbles. Grade III is many bubbles. And lastly, Grade IV has continuous bubbles throughout the cardiac cycle. During the process of decompression, this scale is useful for determining the presence and quantity of bubbles in the divers' blood stream. The decompression process is slowed down if the frequency and quantity of bubbles is too high.

The risk of bubbles passing through the circulation as measured by a Doppler can be classified according to the Spencer scale. The risk increases as the frequency and quantity of bubbles increases. However there is no time frame on the Spencer scale. For example, a Class IV risk for a short time (minutes or seconds) might be enough to cause serious injury or death. But what about a Class I that lasts for two hours? Is the risk cumulative over time? In other words, which is more likely to cause damage in a CPB patient; lots of GME in a short time or a few GME over a long period culminating in a large volume having entered the patient. And once GME composed mostly of nitrogen have entered the patient, how can they be removed?

Bubble Interventions

- Use an arterial bubble trap w/ purge
- CO2 flush the surgical field
- Ask the surgeon to stop what he is doing and fix the bubble source
- Add volume to the venous reservoir
- Slow down the suckers and vent
- Limit perfusionist interventions
- Use a MCA Doppler
- Increase sweep FiO2

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These are the common interventions perfusionists use to prevent or removed GME:

An arterial bubble trap or filter with a purge line physically removes many bubbles from the system, but not all of them.

A CO2 flush of the surgical field will reduce the possibility of sucking nitrogen from the field, either through the venous line or the vent and suckers.

It is not practical to ask the surgeon to stop what he is doing and fix the bubble source unless it is impairing venous return.

Adding volume to the venous reservoir may provide more pressure at the bottom and increase the bubble buoyancy, but only for larger bubbles.

Slowing down the suckers and vent will reduce the entrainment of nitrogen. But this may not be possible at certain times during the course of the surgery.

Gaseous microemboli encapsulated by an albumin membrane (bloody meringue) are difficult to disperse.

Limiting interventions is not practical in certain situations.

A middle cerebral artery Doppler device monitors bubbles going to the brain and can indicate if an intervention to stop them is effective.

Increasing the sweep gas FiO2 through the oxygenator will change the nitrogen bubbles to oxygen bubbles which are much less harmful.

Scenario # 1: Nitrogen Entrainment
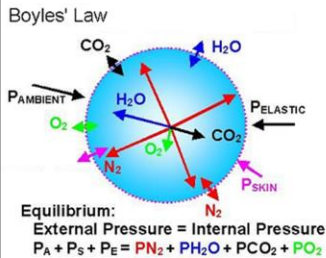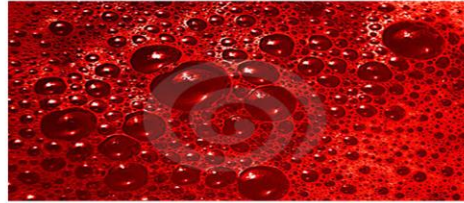Incidental Brain Emboli: Cardiopulmonary Bypass Principles & Practice, Gravlee et al, Ed., 1993, pg 549
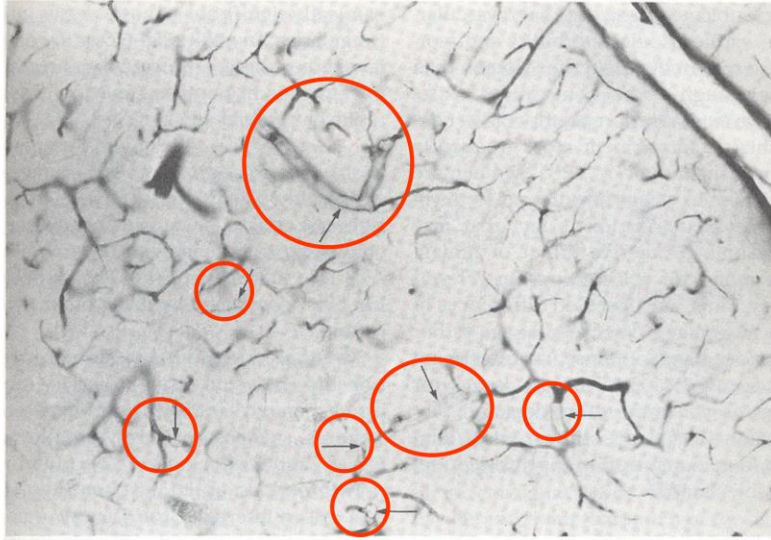
   This photograph of a tissue section taken at autopsy revealed numerous gaseous microemboli (GME) within the capillary system of the cerebral cortex. The patient had undergone heart surgery using CPB, but did not die of embolism. This was an incidental finding. The emboli obstructed many capillaries which reduced blood flow to brain tissue. The GME were still intact several hours after death, implying that their composition was an insoluble gas, probably nitrogen. If the emboli had been primarily oxygen, the bubbles would have been quickly absorbed by the surrounding hypoxic tissues.

Scenario # 1: Nitrogen Entrainment

Circuit air bubbles composition

Vann RD, Butler FK, Mitchell SJ, Moon RE. Decompression illness.
Lancet. 2011 Jan 8;377(9760):153-64.

Boyles' Law

CO_2 H_2O
$P_{AMBIENT}$ H_2O $P_{ELASTIC}$
O_2 CO_2
O_2
N_2 P_{SKIN}
N_2

Equilibrium:
External Pressure = Internal Pressure
$P_A + P_S + P_E = PN_2 + PH_2O + PCO_2 + PO_2$

Gas in the bubble	Pre-oxygenator bubble	Post-oxygenator bubble	Post-oxygenator bubble
	FiO2 = 21%	FiO2 = 40%	FiO2 = 100%
N2	70%	54%	0%
O2	19%	35%	89%
CO2	5%	5%	5%
H2O	6%	6%	6%

Most bubbles that enter the CPB circuit are initially composed of room air. Based on Boyles' Law, the bubbles will equilibrate with the dissolved gas in the surrounding fluid. In this case, the surrounding fluid is venous blood which also contains carbon dioxide. Water vapor will also enter the bubble, making the final composition approximately 70% nitrogen, 19% oxygen, 5% carbon dioxide and 6% water vapor. Thus the bubble will be composed primarily of an insoluble and non-absorbable gas; nitrogen.

If the bubble then passes through an oxygenator using a sweep gas FiO2 of 40%, the nitrogen composition of the bubble will decrease to 54% and the oxygen increase to 35%, but the bulk of the bubble will remain a non-absorbable gas.

However if the bubble were to pass through an oxygenator using a sweep gas of 100% oxygen, the nitrogen content of the bubble would decrease to nothing; the bubble being converted to primarily oxygen. Although oxygen is only slightly more soluble than nitrogen, it is a biologically active gas which means that a living system will quickly absorb it and convert it to carbon dioxide. Even though an oxygen GME can obstruct capillary flow, it will be absorbed in a short time with the subsequent restoration of blood flow.

If the situation is such that excessive air is entering the CPB circuit, the perfusionist can combat the danger of non-absorbable nitrogen GME by converting them to oxygen GME. This is easily done by turning the sweep gas FiO2 to 100% oxygen.

Scenario # 1: Treating Massive Air Entry

1. **During CPB**
   - **Sweep gas: 100% O2 for at least 2 hours**
     - Removes N2 from the tissues & occlusive bubbles
   - **Thiopental**
     - Reduces brain activity, O2 consumption & ICP
   - **Profound hypothermia for 60 minutes**
     - Reduces brain activity & O2 consumption
     - Protects against reperfusion injury
   - **Retrograde cerebral perfusion**
     - Pushes air bubbles out of head vessels ?
2. **After CPB use head injury protocol**
   - Barbiturate coma for up to 96 hours
   - Moderate hypothermia

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If a patient should suffer a massive air embolus on CPB, several steps should be rapidly taken:
1. The sweep gas FiO2 should immediately be increased to 100% oxygen to start off gassing the nitrogen.
2. The patient should be placed in a Trendelenburg position (head down) and, if possible, on his left side (left lateral decubitus position). This positioning helps to trap air in the apex of the ventricle.
3. Thiopental or some other barbiturate should be used to reduce brain activity, oxygen consumption and intracranial pressure.
4. Profound hypothermia should be induced for 60 minutes. This will reduce oxygen consumption. Hypothermia will also increase the solubility of the nitrogen so it can be more easily off gassed. It will also protect against reperfusion injury once the brain capillaries are reopened.
5. After CPB, the head injury protocol of barbiturate coma and moderate hypothermia should be used.

Retrograde cerebral perfusion is of questionable benefit. High antegrade blood flow to the brain with cold, 100% oxygenated blood will probably remove the nitrogen more rapidly and effectively than the slower retrograde venous-to-arterial blood flow.

The anesthesiologist may try to perform carotid compression as the embolus is occurring. But the reaction time would need to be almost instantaneous. Carotid compression is also of questionable benefit and may limit the anesthesiologist's other timely and necessary responses.

Air embolism from the right side of the heart to the left side is often overlooked, but can occur in the presence of an unknown cardiac defect such as on open PFO or PDA or an unrepaired ASD or VSD. The air can enter the right side from an open intravenous or central line, from around the venous cannula purse strings due to siphon or vacuum assist or during a right atriotomy or ventriculotomy.

During a true open heart procedure, the evacuation of air from the left side of the heart before the removal of the aortic cross clamp may be very difficult.

Scenario # 2: Hemodilution
What is the safe dilutional hematocrit on CPB ?

Jonas (Peds) 2003	28%
Mathew 2007	27%
Ranucci 2005	26%
Habib 2005	24%
Karkouti 2005	21%
Groom 2002	20%
Procelewska 2004	19%
Ando 2004	15%
Osawa 2003	12%

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Scenario #2 deals with the oxygen carrying capacity of blood during CPB. Each of these authors has reported successful procedures using hemodilution to varying degrees.

Scenario # 2: Hemodilution
Associated with increased morbidity

- **"..hemodilution..associated with..increased morbidity & mortality."**
  - Habib et al. 2003
- **"..hemodilution..&..(PRBC) transfusion (on CPB)..associated with ARF"**
  - Habib et al. 2005
- **"..association between..degree of..hemodilution..&..ARF"**
  - Karkouti et al. 2005
- **"..hemodilution..is a risk factor for postoperative renal dysfunction.."**
  - Ranucci et al. 2005

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Despite successful procedures using abnormally low hematocrit values, hemodilution has been commonly associated with increased morbidity during CPB.

Scenario # 2: Hemodilution

Should Perfusionists Use a Transfusion Trigger On Cardiopulmonary Bypass?*

- Patients with ≥ 25% hct = 2% mortality[+].
- Patients with ≤ 19% hct = 4% mortality.
- Should 19% be a trigger point?
- Reduce the mortality from 4% to 2%
  - NNT: 90 of every 100 low hematocrit patients.
  - 2 patients survive
  - 88 patients unnecessarily transfused
    - *Grist G. 2009.
    - [+]DeFoe et al. 2001.

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A recent article has reported that CPB patients with nadir hematocrit values ≤19% had two times the mortality of patients with nadir hematocrit values ≥ 24%. Subsequently some perfusionists have suggested that an on-CPB hematocrit of 19% might be a good transfusion trigger point; although the article's authors do not suggest this.

If 19% were used as a trigger point for transfusion to reduce the mortality rate from 4% to 2%, ninety low hematocrit patients is the number needed to treat (NNT) by transfusion to result in two additional survivors. That means that 88/90 patients would receive unnecessary transfusions and its associated risks. A transfusion trigger should be the plan of last resort; all other interventions such as hemoconcentration, hypothermia and hyperoxia being exhausted.

Scenario # 2: Hemodilution

Which patient is at risk of oxygen toxicity or reperfusion injury due to the administration of "too much oxygen"?

- **Perfusion Strategy A**
  - **CPB Patient #1**
  - **70 kg, QB = 5000**
  - **Hgb = 9 gm/dl, Hct ~ 27%**
  - **paO2 = 150 mmHg**
  - **O2 on Hgb = 122 ml/L**
  - **Dissolved O2 = 4.5 ml/L**
  - **Total DO2 = 126.5 ml/L**

- **Perfusion Strategy B**
  - **CPB Patient #2**
  - **70 kg, QB = 5000**
  - **Hgb = 8 gm/dl, Hct ~ 24%**
  - **paO2 = 500 mmHg**
  - **O2 on Hgb = 109 ml/L**
  - **Dissolved O2 = 15 ml/L**
  - **Total DO2 = 124 ml/L**

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Two hypothetical patients with similar weights and calculated blood flow are treated with two different oxygenation strategies. Patient #1 has a hemoglobin of 9 gm/dl. To reduce the risk of oxygen toxicity or reperfusion injury, the paO2 is at only 150 mmHg. This gives a total oxygen delivery, including oxyhemoglobin and dissolved oxygen, of 126.5 mls/L of blood flow. Patient #2 has a hemoglobin of only 8 gm/dl. To improve oxygen delivery, the paO2 is at 500 mmHg. This gives a total oxygen delivery, including oxyhemoglobin and dissolved oxygen, of only 124 mls/L of blood flow. Even though patient #2 has a much higher paO2 than patient #1, the amount of oxygen delivered to patient #2 is less than patient #1.

If patient #1 were to develop a base deficit, the perfusionist may try to increase the oxygen delivery. The blood flow could be increased by 10% (to 5500 mls/min) or the paO2 could be increased to 500 mmHg. Either would increase the oxygen delivery by about 10%. If the blood flow cannot be increased due to circumstances and the paO2 is kept low due to fears of oxygen toxicity the perfusionist has three alternatives: 1) administer a buffer base which may simply mask the acidosis, 2) administer red cells to increase the oxygen delivery but which exposes the patient to transfusion hazards or 3) do nothing until the base deficit increases to an arbitrary limit beyond which intervention (items 1 or 2) must be taken.

By masking the acidosis with buffer base or ignoring it until it exceeds an arbitrary limit of acceptability, the perfusionist allows anoxic tissues to accumulate. At some point during or after cardiopulmonary bypass, these ischemic/hypoxic tissues will be re-oxygenated resulting in a genuine injury from reperfusion that the use of low paO2 values was initially trying to avoid.

The most common reason for acidosis on cardiopulmonary bypass is most likely the formation of an anoxic lethal corner due to a change in perfused capillary density. If blood flow cannot be increased, the best treatment is to address the lethal corner directly by using axial vectors to redistribute oxygen to the anoxic tissues. The administration of buffer base or red cells will not directly address the causative issue of the acidosis; the lethal corner.

If patient #2 were to develop a base deficit, the perfusionist may try to increase the oxygen delivery. The blood flow could be increased by 10% (to 5500 mls/min) but the paO2 is already maximized to 500 mmHg. If the blood flow cannot be increased due to circumstances, then the administration of red cells could be justified. The administration of red cells to patient #1 before applying the axial kick strategy may result in an unnecessary transfusion exposure.
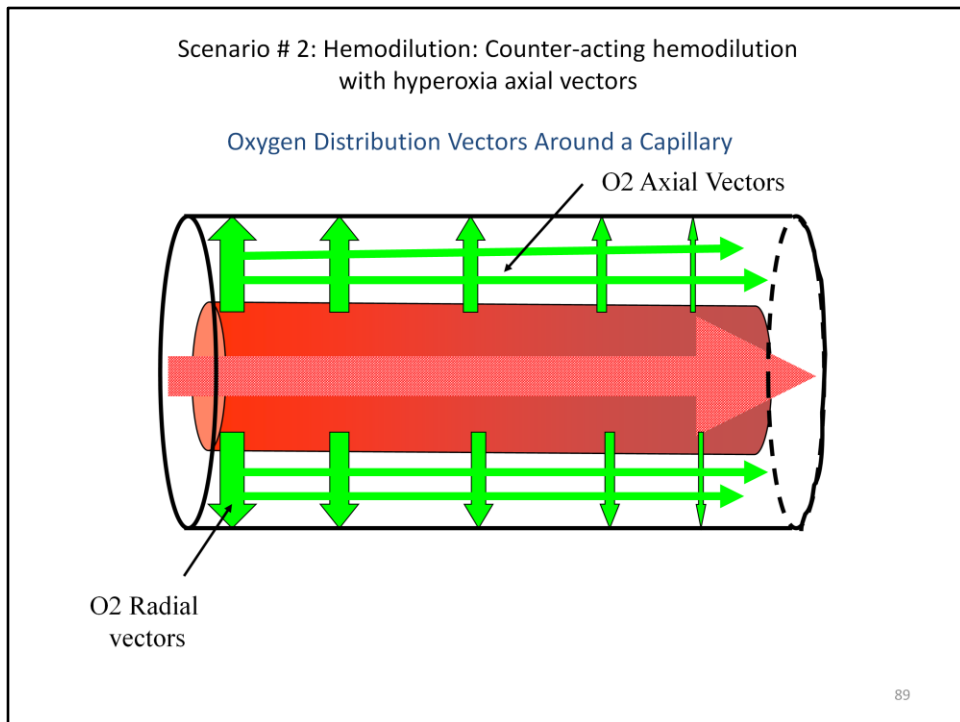
Scenario # 2: Hemodilution

Counter-acting hemodilution with
hyperoxia during major surgery

- **Hyperoxia use in non-cardiac surgery**
  - **Safe**
    - No adverse side effects (human experience)
      - Habler et al. 2002
  - **Reduces the need for transfusion**
    - Less allogenic blood given (human experience)
      - Kemming et al. 2003
  - **Preserves myocardial oxygenation during low hematocrit**
    - Reverses anemic hypoxic ECG changes (human experience)
    - Increases subendocardial O2-delivery 24% (animal study)
      - Kemming et al. 2004
  - **Reverses tissue hypoxia at low hematocrit**
    - Tissue pO2 increases from 10 to 18 mmHg (animal study)
      - Meier eta l. 2004
  - **Reduces risk of wound infection**
    - **Supplemental O2 (80% vs 30%) reduces infections by 39% (human experience)**
      - Brasel et al. 2005

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Hyperoxia is sometimes used for humans in major, non-cardiac surgery and has shown to be safe during many hours under anesthesia with no adverse side effects (Habler et al. 2002). Hyperoxia during surgery reduces the need for allogenic blood transfusion (Kemming et al. 2003). Hyperoxia preserves myocardial oxygenation during low hematocrit and reverses anemic hypoxic ECG changes (human experience). It also increases sub-endocardial oxygen delivery by 24% (animal study) (Kemming et al. 2004). Hyperoxia reverses non-cardiac tissue hypoxia at low hematocrit, increasing the tissue pO2 from 10 to 18 mmHg (animal study) (Meier et al. 2004). Hyperoxia reduces the risk of wound infection. Supplemental O2 (80% vs 30%) reduces wound infections by 39% (human experience) (Brasel et al. 2005), although this aspect is highly controversial.

Scenario # 2: Hemodilution: Counter-acting hemodilution with hyperoxia axial vectors

Oxygen Distribution Vectors Around a Capillary

O2 Axial Vectors

O2 Radial vectors

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In a healthy patient most of the oxygen that enters the tissues moves along radial gradients (illustrated by the perpendicular arrows) between the blood in the capillary and the tissues. Radial gradients radiate at right angles from the central axis of the capillary. The magnitude of these gradients determine the amount and speed that the oxygen enters the tissues. For example, if the paO2of the blood is 150 mmHg and the tissue pO2 at the arterial end of the cylinder averages 37 mmHg, the radial gradient is 113 mmHg. At the venous end, however, the pvO2 of the blood is only 36 mmHg and the tissue pO2 at the venous end of the cylinder averages 9 mmHg, so the radial gradient is only 27 mmHg. This means that more oxygen will move into the arterial end of the Krogh cylinder at a faster rate than at the venous end of the cylinder. This results in an axial oxygen gradient between the arterial-end-tissue and the venous-end-tissues (illustrated by the narrow, horizontal arrows). Axial gradients run parallel to the axis of the capillary within the substance of the tissue sleeve. It has been calculated that 80% of the oxygen entering the venous end of the Krogh cylinder comes from radial gradients and 20% comes from axial gradients if the intra-capillary blood flow velocity is normal (about 200 μ/second).

The development of metabolic acidosis is often closely tied to hemodilution. The reduced oxygen carrying capacity of blood reduces the effectiveness of a normal cardiac output to deliver adequate amounts of oxygen. During CPB, hemodilution can commonly reduce the hemoglobin concentration in the blood by as much as 50%. And yet, perfusionists do not normally compensate by increasing the cardiac output, as the Fick principal would suggest doing:

Normal oxygen delivery: *DO2 = CO X CaO2

With hemodilution, O2 delivery is reduced by 50%: DO2 / 2 = CO X CaO2 / 2

Hemodilution can be compensated by doubling cardiac output: DO2 = [CO X 2] X CaO2 / 2.

Normally perfusionists do not increase blood flow to compensate for hemodilution. As a result, metabolic acidosis is commonly seen during CPB. Augmenting axial oxygen vectors by increasing the sweep gas FiO2 can compensate for this and often reverse the development of a base deficit during CPB.

*DO2 = oxygen delivery, CO = cardiac output, CaO2 = the content of oxygen in the arterial blood

Scenario #3: Metabolic Acidosis: Decreased Perfused Capillary Density
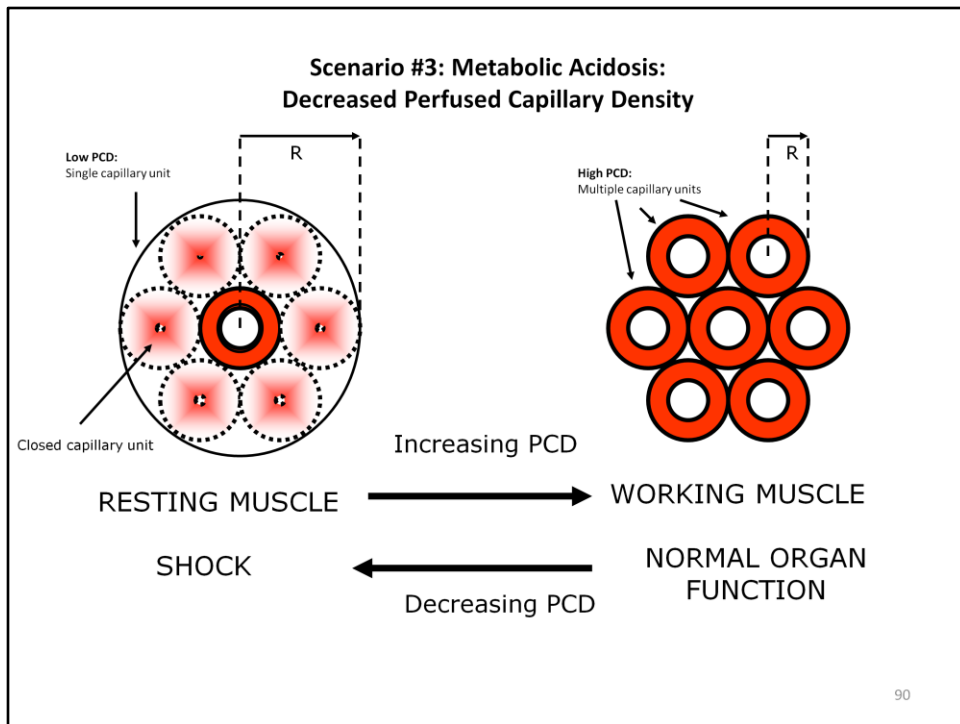
During cardiopulmonary bypass, perfused capillary density (PCD) can change. Normally skeletal muscles are not in use, therefore their PCD remains low without any detrimental effects. However organ systems must still function. Should PCD be reduced due to loss of pulsatility or iatrogenically reduced blood flow, the organ systems can go into shock resulting in metabolic acidosis even though the patient is on CPB.

Scenario #3: Metabolic Acidosis: The Anoxic Lethal Corner
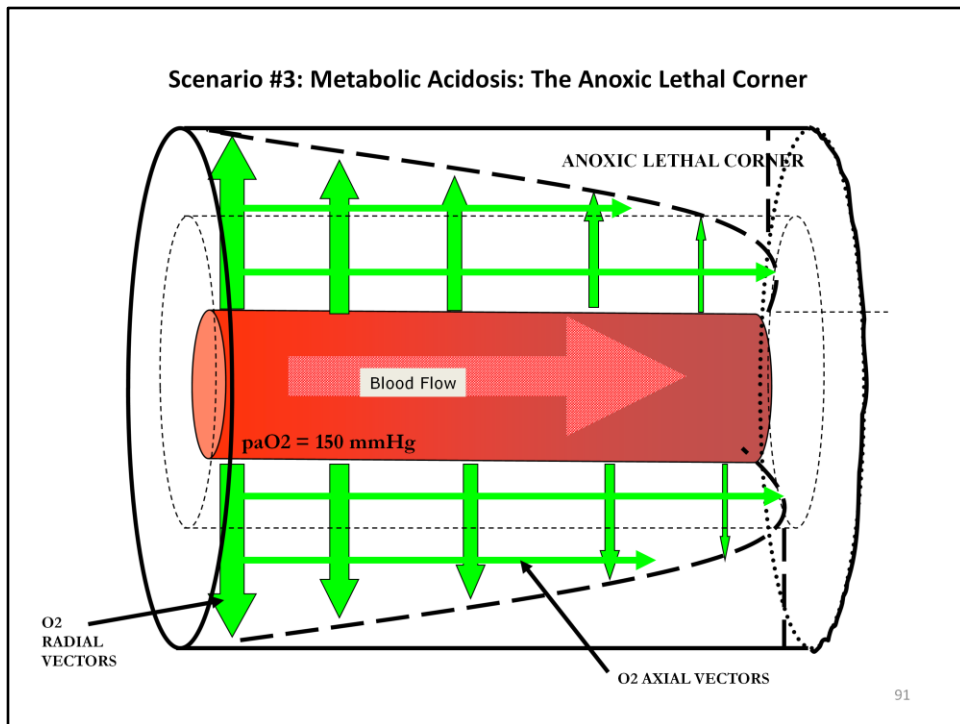
When intracapillary blood flow velocity is reduced below normal the result is a reduction in perfused capillary density and venous blood that has a lower than normal pvO2 concentration (the SVO2 falls below normal). The oxygen concentration in the venous end of the Krogh cylinder falls below normal. However the arterial end tissues still receive adequate amounts of oxygen. This causes an increase in the axial gradient, pushing more oxygen towards the lethal corner area that has developed due to the de-saturated venous blood.
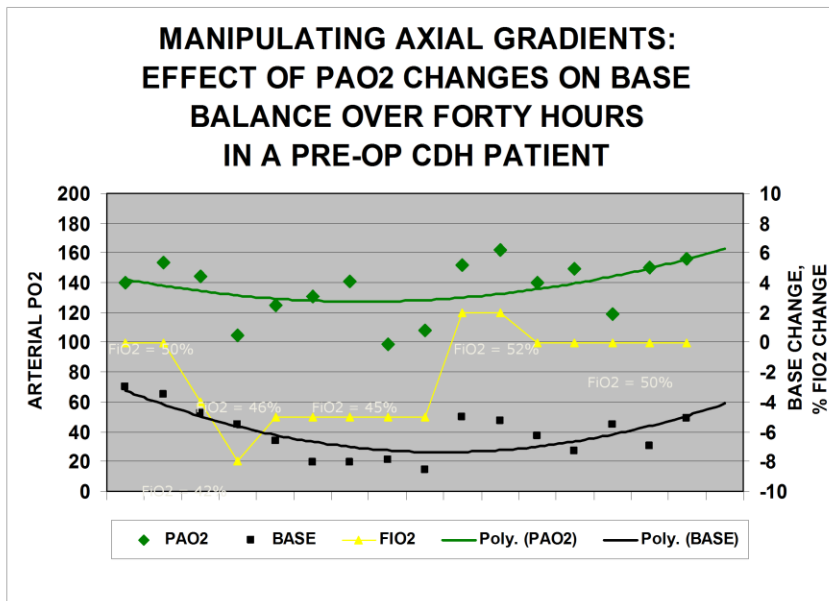
As intracapillary blood flow velocity falls, less oxygen comes from radial vectors and more comes from axial vectors. By the time that intra-capillary blood flow velocity reaches 25% of normal, 80% of the oxygen entering the venous end of the Krogh cylinder comes from axial vectors and only 20% comes from radial vectors. That's not to say that there is adequate oxygenation at the venous end; only that most of the oxygen entering the venous end comes from axial vectors under these strenuous conditions.

Scenario #3: Metabolic Acidosis: Axial kick & increased oxygenation to the lethal corner
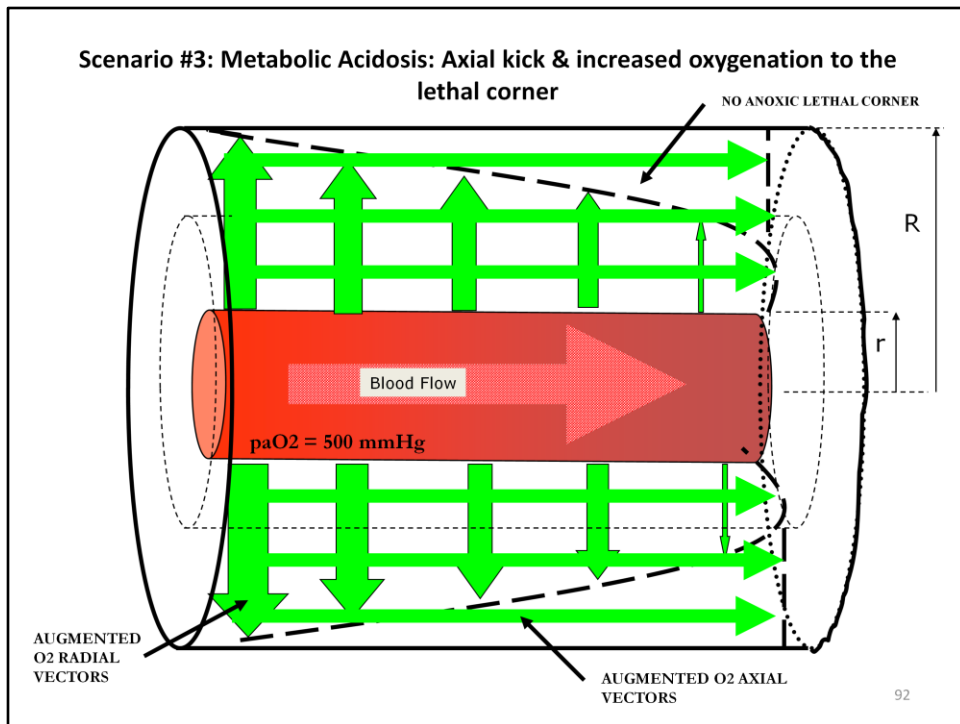
During periods of low blood flow it is possible to capitalize on the increased axial vectors by greatly increasing the paO2. In this example, increasing the paO2 from 150 to 500 mmHg floods the arterial end tissues with oxygen. This greatly increases the axial vectors and pushes more oxygen towards the lethal corner. Traditionally it has been taught that increasing the paO2 above the point of full hemoglobin oxygen saturation (about 150 mmHg) is unnecessary because the higher paO2 values only represent miniscule amounts of dissolved oxygen. But by increasing the axial gradient, oxygen can be more effectively redistributed along axial vectors to lethal corner areas during periods of hemodilution, low blood flow or reduced perfused capillary density.

However even if the patient can be stabilized using axial kick to oxygenate the anoxic lethal corner, this will only work for a short periods of time typical of normal CPB applications. In long term support applications, the patient will eventually expire as a result of the build up of carbon dioxide in the lethal corner.

Scenario #3: Metabolic Acidosis: Clinical Presentation

MANIPULATING AXIAL GRADIENTS: EFFECT OF PAO2 CHANGES ON BASE BALANCE OVER FORTY HOURS IN A PRE-OP CDH PATIENT

This example shows that even minor changes in the axial gradient can effect oxygenation in a lethal corner. This diaphragmatic hernia patient required epinephrine, dopamine and dobutamine at high levels soon after birth to maintain hemodynamics and oxygenation. However during the time period shown in this example, only 5 μ/min/kg of dopamine was in use and the patient was stable hemodynamically.

Over the 40 hour period shown here, the ventilator FiO2 was actively weaned from 50% to 42%, back to 45%, then 52% and finally back to 50%. As the paO2 trended downward due to weaning of the FiO2, the axial gradients were reduced allowing the development of an anoxic lethal corner. Metabolic acidosis developed and the base deficit increased. When the FiO2 was again increased the axial gradients also increased and the metabolic acidosis and base deficit were reduced.

Starting from arterial pO2 values of 140 ~160 mmHg, the lowest paO2 value achieved as the ventilator FiO2 was weaned from 50% to 42% was ~100 mmHg. In a patient such as this with marginal capillary redundancy a reduction of approximately 50 mmHg in the paO2 can significantly reduce the axial gradient which, in turn would allow the formation of an anoxic lethal corner. The patient became acidotic and developed a base deficit even though the paO2 never dropped below 98 mmHg and the arterial O2 saturation never dropped below 95%. Returning the FiO2 to 50% restored the paO2 to the 140~160 mmHg range. This improved the base deficit by restoring the axial gradient and eliminating the lethal corner.

Some clinicians might consider this as a failure of the patient to tolerate the weaning of the ventilator FiO2 even though the SaO2 never dropped below 95%. But the only failure here was the failure to recognize that the patient had marginal systemic perfused capillary density and needed additional pharmacologic cardiac support to improve capillary redundancy before FiO2 weaning could proceed.

Scenario #3: Metabolic Acidosis: paO2 = 150 mmHg
Axial kick oxygenates the distal capillary tissues
preventing the formation of a lethal corner
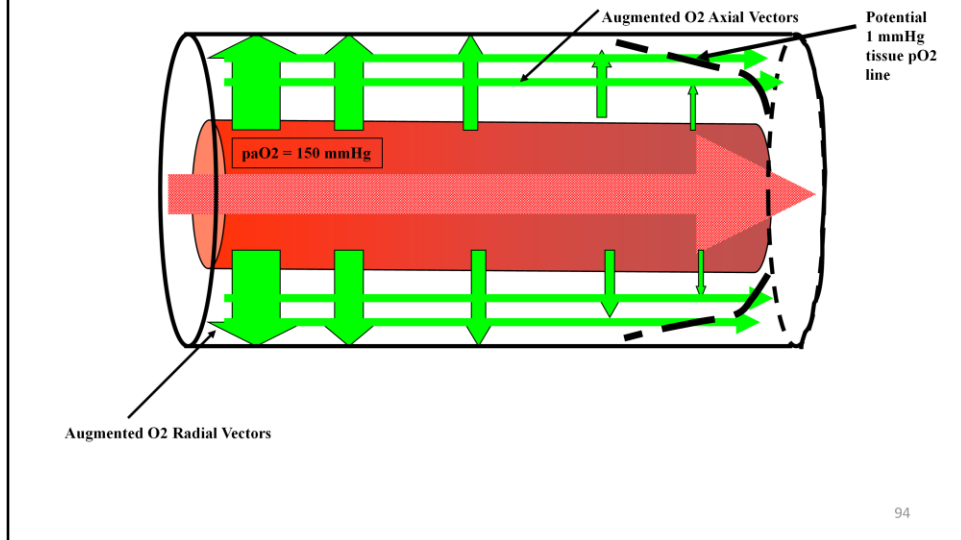
To illustrate the previous example using the Krogh cylinder model, the patient had an arterial paO2 of about 150 mmHg and no base deficit. Since the patient was still experiencing some degree of shock, axial vectors were needed to augment oxygenation to the distal cylinder

Scenario #3: Metabolic Acidosis: paO2 = 100 mmHg
Reduced axial kick causes formation of a lethal corner
and a base deficit develops
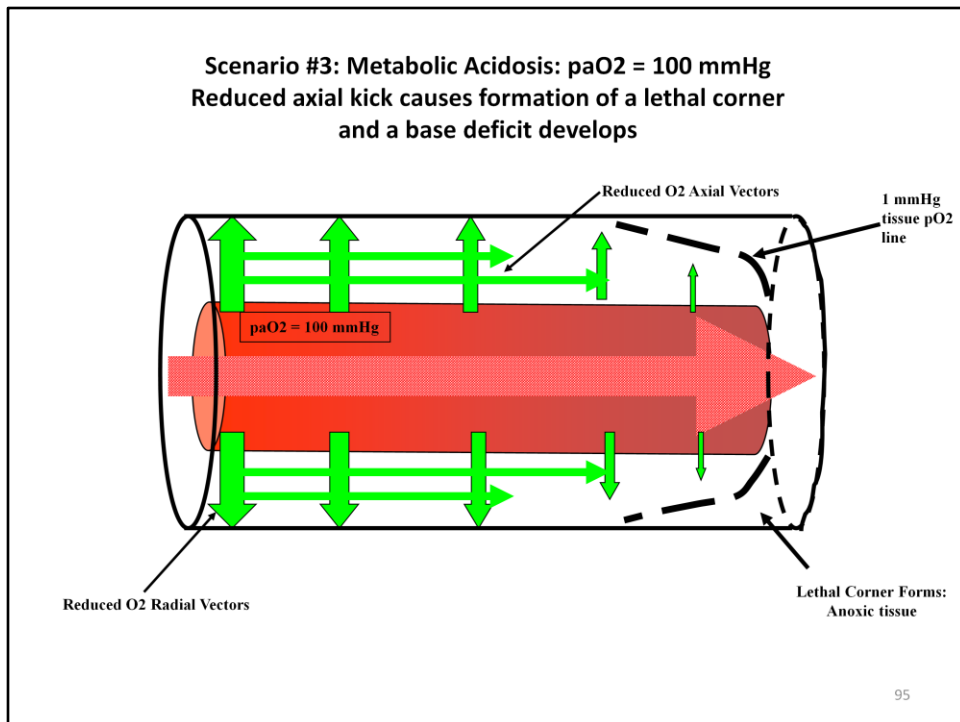
As the ventilator FiO2 was reduced, the arterial paO2 dropped to approximately 100 mmHg. This resulted in a reduction of axial vectors and the formation of an anoxic lethal corner. Metabolic acidosis started in the lethal corner and the patient developed an increased base deficit. Upon subsequently increasing the ventilator FiO2, the arterial paO2 was restored to approximately 150 mmHg and the lethal corner was again obliterated by axial vectors of oxygen

Scenario # 4: Deep Hypothermic Circulatory Arrest:
The Need for Dissolved Oxygen

- Hemodilution reduces DO2
- Hypothermia impairs O2 offloading
- Hyperoxia provides dissolved O2
  - "Dissolved oxygen satisfies most of the brain's oxygen requirements during profound hypothermic cardiopulmonary bypass."
    - Dexter et al. 1997

Temperature vs. Cerebral Metabolic Rate
(Data from McCullough, Zhang, Reich, et. al., 1999)
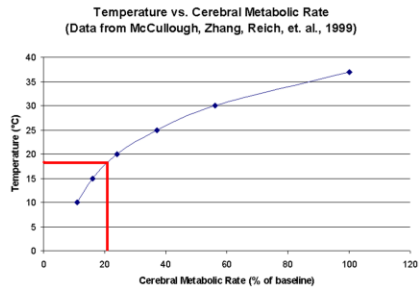
As the body and blood are cooled during CPB, the metabolic rate is reduced. At 18°C the metabolic rate is thought to be about 10% of normal. However experiments have shown that cerebral metabolism is considerably higher at 18°C than once thought. Other problems complicate the cooling process. Hemodilution reduces oxygen delivery. Hypothermia impairs the release of oxygen from the remaining oxyhemoglobin. The p50 indicates the ability of the hemoglobin to release oxygen in relation to the tissue oxygen concentration. At 37°C, the p50 of hemoglobin is 27 mmHg and the average tissue pO2 is also about 27 mmHg. At 18°C, the p50 is only about 7 mmHg, meaning that the tissue pO2 value must fall to an average of 7 mmHg to force the transfer of oxygen from the hemoglobin to the tissues. The reduction in CO2 production further reduces the release of oxygen from the blood. Hemoglobin becomes essentially nonfunctional for oxygen exchange at profound temperatures unless the tissue oxygen concentration drops to extremely low levels.

However as blood cools, oxygen becomes more soluble. Once the hemoglobin is fully saturated a considerable amount of dissolved oxygen can be carried by the blood if it is exposed to a high FiO2 sweep gas. Dissolved oxygen is not limited by the effects of cold hemoglobin and is therefore available to any needy tissues.

- "Used prior to DHCA normoxic CPB increases brain damage compared to hyperoxic CPB. The mechanism is hypoxic injury, which overwhelms any injury caused by oxygen free radicals."

  – Nollert G, Nagashima M, Bucerius J, et al. Oxygenation strategy and neurologic damage after deep hypothermic circulatory arrest. II. hypoxic versus free radical injury. J Thorac Cardiovasc Surg 1999;117:1172-9.

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Nollert G, Nagashima M, Bucerius J, et al. Oxygenation strategy and neurologic damage after deep hypothermic circulatory arrest. II. hypoxic versus free radical injury. J Thorac Cardiovasc Surg 1999;117:1172-9.

OBJECTIVES: Laboratory studies suggest that myocardial reperfusion injury is exacerbated by free radicals when pure oxygen is used during cardiopulmonary bypass. In phase I of this study we demonstrated that normoxic perfusion during cardiopulmonary bypass does not increase the risk of microembolic brain injury so long as a membrane oxygenator with an arterial filter is used. In phase II of this study we studied the hypothesis that normoxic perfusion increases the risk of hypoxic brain injury after deep hypothermia with circulatory arrest.

METHODS: With membrane oxygenators with arterial filters, 10 piglets (8-10 kg) underwent 120 minutes of deep hypothermia and circulatory arrest at 15 degrees C, were rewarmed to 37 degrees C, and were weaned from bypass. In 5 piglets normoxia (PaO_2 64-181 mm Hg) was used during cardiopulmonary bypass and in 5 hyperoxia (PaO_2 400-900 mm Hg) was used. After 6 hours of reperfusion the brain was fixed for histologic evaluation. Near-infrared spectroscopy was used to monitor cerebral oxyhemoglobin and oxidized cytochrome a,a3 concentrations.

RESULTS: Histologic examination revealed a significant increase in brain damage in the normoxia group (score 12.4 versus 8.6, $P = .01$), especially in the neocortex and hippocampal regions. Cytochrome a,a 3 and oxyhemoglobin concentrations tended to be lower during deep hypothermia and circulatory arrest in the normoxia group ($P = .16$).

CONCLUSIONS: In the setting of prolonged deep hypothermia and circulatory arrest with membrane oxygenators, normoxic cardiopulmonary bypass significantly increases histologically graded brain damage with respect to hyperoxic cardiopulmonary bypass. Near-infrared spectroscopy suggests that the mechanism is hypoxic injury, which presumably overwhelms any injury caused by increased oxygen free radicals.

Scenario # 4: Deep Hypothermic Circulatory Arrest
Oxygen (and Nitrogen) Loading Tissues

ESTIMATED AVERAGE TISSUE PO2

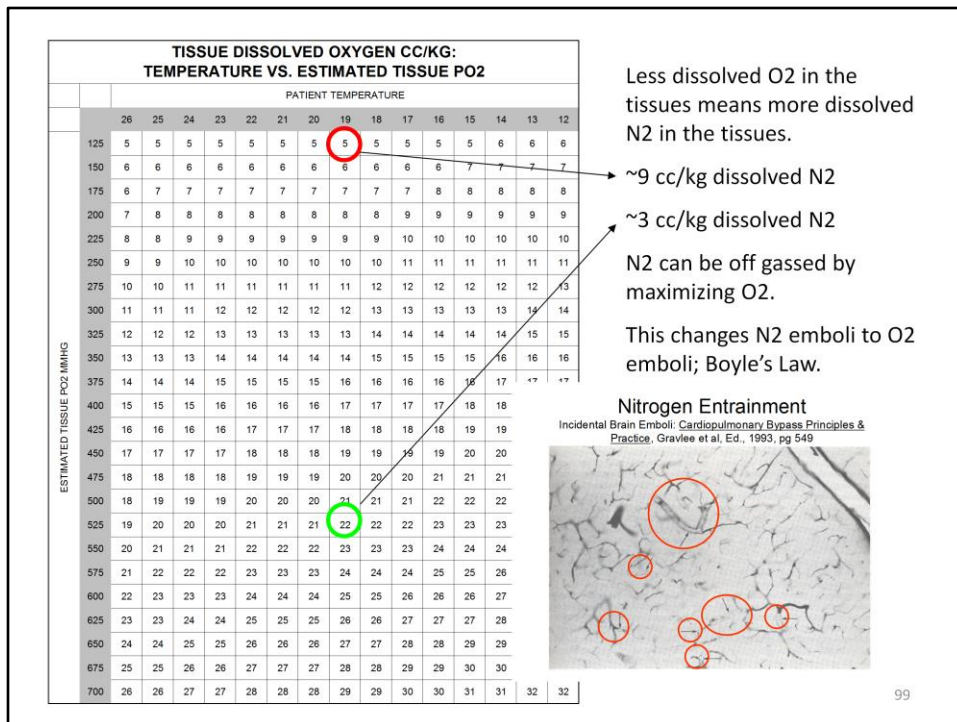| VENOUS PO2 MMHG	ARTERIAL PO2 MMHG														
	200	**250**	**300**	**350**	**400**	**450**	**500**	**550**	**600**	**650**	**700**	**750**	**800**	**850**	**900**
50	125	150	175	200	225	250	275	300	325	350	375	400	425	450	475
100	150	175	200	225	250	275	300	325	350	375	400	425	450	475	500
150		200	225	250	275	300	325	350	375	400	425	450	475	500	525
200			250	275	300	325	350	375	400	425	450	475	500	525	550
250				300	325	350	375	400	425	450	475	500	525	550	575
300					350	375	400	425	450	475	500	525	550	575	600
350						400	425	450	475	500	525	550	575	600	625
400							450	475	500	525	550	575	600	625	650
450								500	525	550	575	600	625	650	675
500									550	575	600	625	650	675	700

Dissolved nitrogen

The solubility of oxygen in saline increases from 0.03 ml/mmHg/L to 0.042 ml/mmHg/L as the body temperature drops from 37C to 18C, an increased dissolved content of 40%. Over the same temperature range overall oxygen consumption drops to 10% of normal (20% in the brain). So prior to profound hypothermic arrest the amount of dissolved oxygen in the tissues can be increased substantially by increasing the paO2 of the blood coming from the oxygenator. Since the hemoglobin is essentially non-functional at this temperature, an estimate of the dissolved tissue oxygen can be derived by averaging the paO2 and the pvO2.

For example, at 18C a paO2 of 200 mmHg and a pvO2 of 50 mmHg the average tissue pO2 would be 125 mmHg: (200 mmHg + 50 mmHg) ÷ 2 = 125 mmHg. Correspondently the amount of nitrogen dissolved in the tissues would be an average of 625 mmHg.

Alternatively at 18C a paO2 of 750 mmHg and a pvO2 of 300 mmHg the average tissue pO2 would be 525 mmHg: (750 mmHg + 300 mmHg) ÷ 2 = 525 mmHg. But the nitrogen dissolved in the tissues would only be 225 mmHg.

This means that over four times as much oxygen can be dissolved in the brain at 18C if a paO2 of 750 mmHg is infused and the pvO2 reaches 300 mmHg. Targeting a pvO2 of 300+ mmHg assures that the tissues are well loaded with dissolved oxygen prior to circulatory arrest.
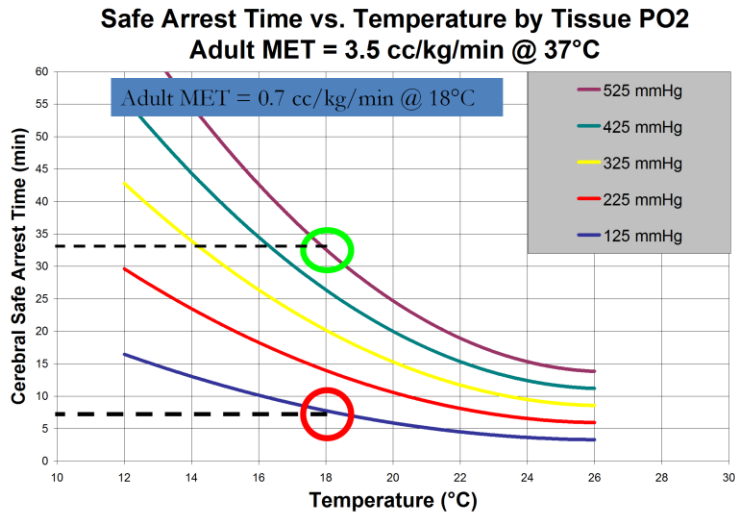
If the perfusionist chooses not to load oxygen by using a lower FiO2, then, by default, s/he is loading nitrogen into the cold tissues. Like oxygen, nitrogen is more soluble at lower temperatures. During rewarming, nitrogen (like oxygen) will tend to come out of solution and form bubbles in the blood vessels, stroma or even the parenchyma of the organs. Because nitrogen is an inert gas and will not be consumed by the living tissues, nitrogen bubbles can block or compress vital capillaries for extended periods.

TISSUE DISSOLVED OXYGEN CC/KG:
TEMPERATURE VS. ESTIMATED TISSUE PO2

PATIENT TEMPERATURE (top header) / ESTIMATED TISSUE PO2 MMHG (left header)

	26	25	24	23	22	21	20	19	18	17	16	15	14	13	12
125	5	5	5	5	5	5	5	5	5	5	5	5	6	6	6
150	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7
175	6	7	7	7	7	7	7	7	7	7	8	8	8	8	8
200	7	8	8	8	8	8	8	8	8	9	9	9	9	9	9
225	8	8	9	9	9	9	9	9	9	10	10	10	10	10	10
250	9	9	10	10	10	10	10	10	10	11	11	11	11	11	11
275	10	10	11	11	11	11	11	11	12	12	12	12	12	12	13
300	11	11	11	12	12	12	12	12	13	13	13	13	13	14	14
325	12	12	12	13	13	13	13	13	14	14	14	14	14	15	15
350	13	13	13	14	14	14	14	14	15	15	15	16	16	16	
375	14	14	14	15	15	15	15	16	16	16	16	17	17	17	
400	15	15	15	16	16	16	16	17	17	17	17	18	18		
425	16	16	16	16	17	17	17	18	18	18	18	19	19		
450	17	17	17	17	18	18	18	19	19	19	19	20	20		
475	18	18	18	18	19	19	19	20	20	20	21	21	21		
500	18	19	19	19	20	20	20	21	21	21	22	22	22		
525	19	20	20	20	21	21	21	22	22	22	23	23	23		
550	20	21	21	21	22	22	22	23	23	23	24	24	24		
575	21	22	22	22	23	23	23	24	24	24	25	25	26		
600	22	23	23	23	24	24	24	25	25	26	26	26	27		
625	23	23	24	24	25	25	25	26	26	27	27	27	28		
650	24	24	25	25	26	26	26	27	27	28	28	29	29		
675	25	25	26	26	27	27	27	28	28	29	29	30	30		
700	26	26	27	27	28	28	28	29	29	30	30	31	31	32	32

Less dissolved O2 in the tissues means more dissolved N2 in the tissues.

~9 cc/kg dissolved N2

~3 cc/kg dissolved N2

N2 can be off gassed by maximizing O2.

This changes N2 emboli to O2 emboli; Boyle's Law.

Nitrogen Entrainment
Incidental Brain Emboli: Cardiopulmonary Bypass Principles & Practice, Gravlee et al, Ed., 1993, pg 549

An average tissue pO2 of only 125 mmHg at 18C that translates to 5cc/kg of dissolved oxygen and 9cc/kg of dissolved nitrogen. However if the tissue pO2 is 525 mmHg at 18C that translates to 22cc/kg of dissolved oxygen and only 3cc/kg of dissolved nitrogen.

If less oxygen is loaded into cold tissues, by default, more nitrogen is loaded. Removing this nitrogen during rewarming can be problematic. Rewarming decreases the solubility of nitrogen. Similarly nitrogen becomes less soluble in a diver rising from the depths as the pressure decreases. During the ascent (or rewarming) nitrogen bubbles can form causing 'the bends'. As rewarming progress, nitrogen bubbles can form in the tissues before it diffuses into the capillaries. The potential also exists for nitrogen bubbles to form within capillaries, potentially blocking the blood flow as depicted in the above photo.
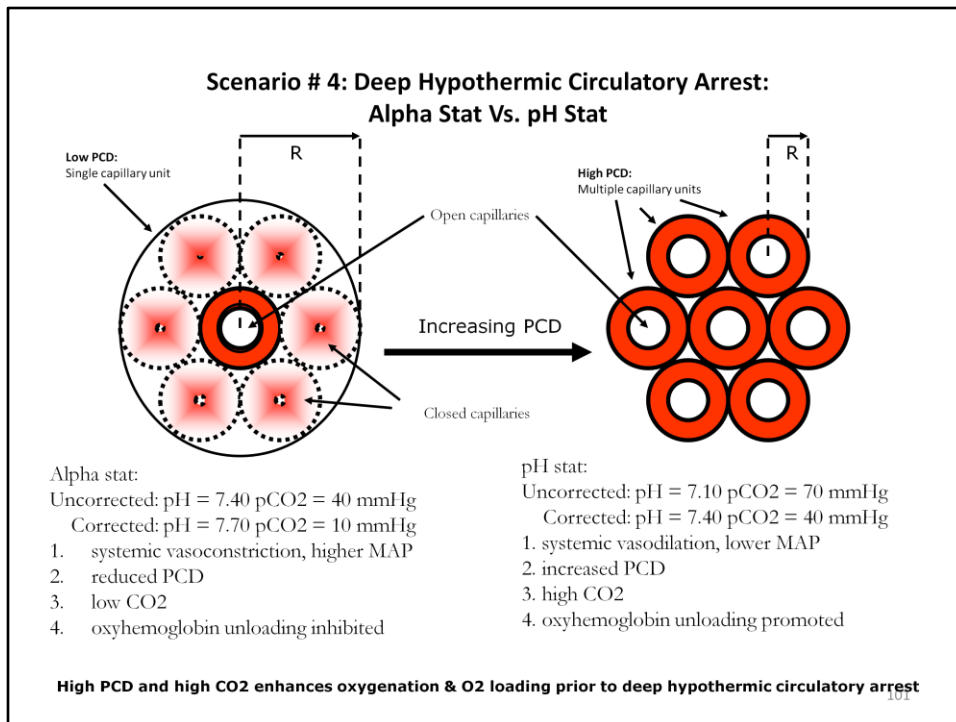
Scenario # 4: Deep Hypothermic Circulatory Arrest
Extending the safe arrest time

Safe Arrest Time vs. Temperature by Tissue PO2
Adult MET = 3.5 cc/kg/min @ 37°C

Adult MET = 0.7 cc/kg/min @ 18°C

- 525 mmHg
- 425 mmHg
- 325 mmHg
- 225 mmHg
- 125 mmHg

Cerebral Safe Arrest Time (min) vs *Temperature (°C)*

   The metabolic equivalent (MET) is a physiological concept expressing the energy cost of physical activities as multiples of the resting metabolic rate which is 3.5cc O2/kg/min in adults*. For example, an adult just sitting still would have a MET of 1. During exercise the same adult may be using 5 METs (17.5cc O2/kg/min). However during profound hypothermic arrest, the overall MET drops to 10% of the metabolic rate; 0.35 ccO2/kg/min. In the brain the MET only drops to 20%; 0.7 ccO2/kg/min.
   Based on an average tissue pO2 of 125 mmHg at 18C (~ 5 cc/L of dissolved O2), the safe arrest time would be approximately 7 minutes before the brain consumed all the dissolved oxygen and converted to anaerobic metabolism. During anaerobic metabolism, the brain becomes acidotic and increasingly susceptible to reperfusion injury when perfusion is restored. However based on an average tissue pO2 of 525 mmHg at 18C (~ 22 cc/L of dissolved O2), the safe arrest time would be approximately 31 minutes before the brain consumed all the dissolved oxygen and converted to anaerobic metabolism. This extended safe arrest time reduces the risk of reperfusion injury when blood flow is re-established.
   *Infants have a higher base MET; 6cc O2/kg/min.

Scenario # 4: Deep Hypothermic Circulatory Arrest: Alpha Stat Vs. pH Stat

Low PCD: Single capillary unit

R

Open capillaries

High PCD: Multiple capillary units

R

Increasing PCD

Closed capillaries

Alpha stat:
Uncorrected: pH = 7.40 pCO2 = 40 mmHg
    Corrected: pH = 7.70 pCO2 = 10 mmHg
1. systemic vasoconstriction, higher MAP
2. reduced PCD
3. low CO2
4. oxyhemoglobin unloading inhibited

pH stat:
Uncorrected: pH = 7.10 pCO2 = 70 mmHg
    Corrected: pH = 7.40 pCO2 = 40 mmHg
1. systemic vasodilation, lower MAP
2. increased PCD
3. high CO2
4. oxyhemoglobin unloading promoted

High PCD and high CO2 enhances oxygenation & O2 loading prior to deep hypothermic circulatory arrest

During alpha stat control, the degree of ionization (alpha) of the imidazole groups of intracellular proteins is thought to remain constant despite the change in temperature. This tends to buffer the intracellular pH within a normal, neutral range. In order to accomplish this, the carbon dioxide must remain at a constant level in the blood and tissues. Usually this means that sweep gas ventilation is matched to the same speed as the oxygenator blood flow. The resultant blood gas will read within the normal range without temperature correction at any temperature between 37C and 15C. Alpha stat control also tends to constrict the systemic arteries, particularly cerebral arteries. It also inhibits O2 disassociation from hemoglobin due to the low CO2 concentrations available to form carboxyhemoglobin which displaces the oxygen from the hemoglobin.

A pH stat control aims to maintain a temperature corrected pH of 7.4 at the lower temperatures of hypothermic cardiac bypass. This is achieved by having a pCO2 level which is higher than that required for alpha-stat management. From the alpha stat point of view, pH-stat management results in a respiratory acidosis at lower temperatures. Other effects include systemic arterial dilation, particularly in the cerebral arteries, and enhanced oxygen unloading from hemoglobin. Since more capillaries are open using pH stat, more oxygen can be dissolved in brain tissue during cooling. So pH stat control is better able to oxygen load a patient in anticipation of deep hypothermic circulatory arrest.

In general, adult patients seem to fair better when alpha stat control is used during routine cardiopulmonary bypass (CPB). "Fair better" means that there is less of a tendency to develop a base deficit during CPB. Pediatric patients tend to fair better using pH stat control. But there may be some variation in age groups. Adults who develop a base deficit during alpha stat control may fair better if pH stat control is implemented. The same is true of pediatric patients who develop a base deficit during pH stat control, with the base deficit stopping or reversing when alpha stat control is implemented.

Scenario # 4: Deep Hypothermic Circulatory Arrest:
Acid produced during 60 minutes @ 18°C
(Pearl et al 2000)

Normoxia = pvO2 <150 mmHg
Hyperoxia = pvO2 > 300 mmHg

	Alpha stat Normoxia	pH stat Normoxia	Alpha stat Hyperoxia	pH stat Hyperoxia
	Lo CO2 Lo O2	Hi CO2 Lo O2	Lo CO2 Hi O2	Hi CO2 Hi O2
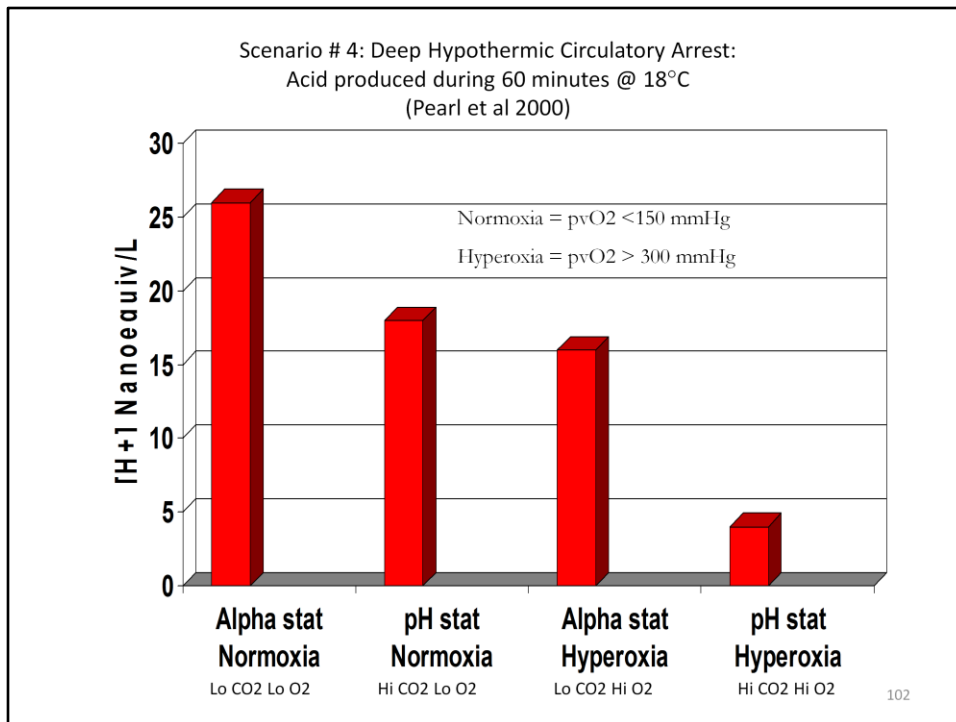
High perfused capillary density (PCD) and oxygen loading can reduce the development of acidosis during the period of hypothermia arrest. There are four discrete gas strategies that perfusionists can employ to prepare the patient for deep hypothermia circulatory arrest (DHCA); 2 for carbon dioxide and 2 for oxygen:
1.Low CO2 content (Alpha stat) maintains a higher perfusion pressure but causes systemic vasoconstriction and reduced PCD.
2.High CO2 content (pH stat) results in lower perfusion pressure but causes systemic vasodilatation that increases PCD.
3.Low dissolved O2 content (normoxia) is thought to reduce the formation of super oxide radials but limits the ability to oxygen load tissues.
4.High dissolved O2 content (hyperoxia) is thought to increase the formation of super oxide radicals but greatly increases tissue oxygen loading.

Pearl JM, Thomas DW, Grist G, Duffy JY, Manning PB. Hyperoxia for management of acid-base status during deep hypothermia with circulatory arrest. Ann Thorac Surg 2000;70:751-5.
BACKGROUND: Which blood gas strategy to use during deep hypothermic circulatory arrest has not been resolved because of conflicting data regarding the advantage of pH-stat versus alpha-stat. Oxygen pressure field theory suggests that hyperoxia just before deep hypothermic circulatory arrest takes advantage of increased oxygen solubility and reduced oxygen consumption to load tissues with excess oxygen. The objective of this study was to determine whether prevention of tissue hypoxia with this strategy could attenuate ischemic and reperfusion injury.
METHODS: Infants who had deep hypothermic circulatory arrest (n = 37) were compared retrospectively. Treatments were alpha-stat and normoxia (group I), alpha-stat and hyperoxia (group II), pH-stat and normoxia (group III), and pH-stat and hyperoxia (group IV).
RESULTS: Both hyperoxia groups had less acidosis after deep hypothermic circulatory arrest than normoxia groups. Group IV had less acid generation during circulatory arrest and less base excess after arrest than groups I, II, or III (p < 0.05). Group IV produced only 25% as much acid during deep hypothermic circulatory arrest as the next closest group (group II).
CONCLUSIONS: Hyperoxia before deep hypothermic circulatory arrest with alpha-stat or pH-stat strategy demonstrated advantages over normoxia. Furthermore, pH-stat strategy using hyperoxia provided superior venous blood gas values over any of the other groups after circulatory arrest.

Scenario #5: Oxygen Toxicity
Definition

- Oxygen toxicity occurs when <u>antioxidants are active</u> and perfusion is unimpaired, but there is too much oxygen available for ROS to be controlled.
  - AOX = antioxidants
  - ROS = reactive oxygen species
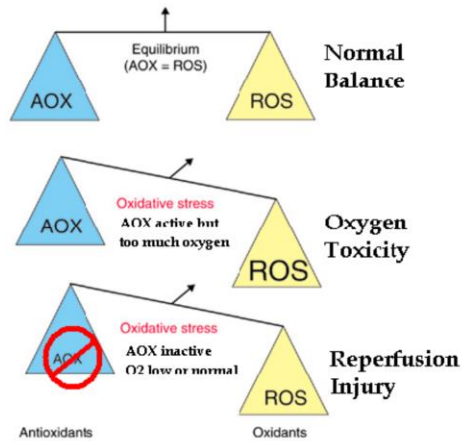
Oxygen toxicity occurs when antioxidants are actively functioning and perfusion is unimpaired, but there is too much oxygen available for reactive oxygen species (ROS) to be controlled. In the medical setting, the most common risk for oxygen toxicity occurs when patients are on mechanical ventilation using high oxygen concentrations for extended periods (days to weeks). The antioxidants in the lung tissues become exhausted and ROS damages the lung tissues.

Scenario #5: Oxygen Toxicity
Develops slowly

- "Because of the effective defense systems *(functioning antioxidants),* the tolerance of viable human cells to *(reactive oxygen species)* is relatively high."
    - Bauer & Bauer. 1999

Bauer V, Bauer F. Reactive oxygen species as mediators of tissue protection and injury. Gen Physiol Biophys 1999;18 Spec No:7-14.

Extensive research efforts during the last three decades resulted in a large body of experimental evidence that suggests an important role of the disbalance between generation and elimination of the oxygen and xenobiotic derived free radicals in physiological and pathological processes. Reactive oxygen species (ROS) are generated in many metabolic pathways, and are entering the organisms from exogenous sources, dominantly via airways and gut. ROS induced injuries, e.g. thermal, chemical, radiation, ischaemia/reperfusion, inflammation, hyperoxia, etc., result in diseases like atherosclerosis, ulcerative colitis, autoimmune diseases, asthma, etc. The current paper is designed to provide an overview of the effects ROS may exert in various tissues. Because of the effective defense systems, the tolerance of viable human cells to ROS is relatively high. The oxidant stress induced dysfunction of various systems, such as the gut, airways, nervous, cardiovascular system, etc., involve both direct and indirect mechanisms. Understanding of these molecular mechanisms is essential for a rational antioxidant therapy.

Scenario # 5: Oxygen Toxicity
Combating toxicity

- The "Oxygen Clock" provides temporal safety from CNS and pulmonary complications due to hyperoxia.
  - NOAA Diving Manual

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    The oxygen clock is a method of monitoring oxygen exposure over time. When diving at oxygen partial pressures above 0.5 atmospheres absolute (ATA) for long periods of time it becomes important to monitor oxygen exposure. At sea level the pO2 of 0.5 ATA of oxygen is 380 mmHg. At a depth of 33 feet, 0.5 ATA of oxygen equals 760 mmHg. At a depth of 99 feet, 0.5 ATA of oxygen equals 1520 mmHg. Over time, the constant exposure to elevated partial pressures of oxygen is detrimental to the pulmonary and central nervous system of a diver. The theory behind the oxygen clock has been around for about 30 years and concerns cerebral and pulmonary oxygen toxicity. The oxygen tolerance unit (OTU) measures the degree of exposure to dangerous levels of oxygen. The OTU is based on empirical data from which the following best fit formula has been derived:

$$OTU = t \left[\left[(PO2 - 0.5) / 0.5 \right] ^{0.83} \right]$$

where:
t = the exposure time in minutes
PO2 = the partial pressure of oxygen in ATA
0.5 = the threshold below which no significant pulmonary oxygen toxicity has been observed
0.83 = the exponent which gives the best fit to experimental observations.

Scenario # 5: Oxygen Toxicity & Air breaks
Off gassing to remove nitrogen from microemboli in the body and resetting the "oxygen clock"

Bubble

- Five minute 'air breaks' taken intermittently restore antioxidant reserve capacity

- Reduces CNS and pulmonary complications.
  - U.S Navy Diving Manual. 1991

US NAVY TREATMENT TABLE 5 - OXYGEN TREATMENT OF TYPE 1 DECOMPRESSION SICKNESS					
PRESSURE	TIME (min)	MEDIA	pO2 mmHg	pN2 mmHg	TOTAL TIME (hrs:min)
3 ATM	20	100% O2	2280	0	0:20
3 ATM	5	AIR	479	1801	0:25
3 ATM	20	100% O2	2280	0	0:45
3-2 ATM	30	100% O2	2280 - 1520	0	1:15
2 ATM	5	AIR	319	1201	1:20
2 ATM	20	100% O2	1520	0	1:40
2 ATM	5	AIR	319	1201	1:45
2-1 ATM	30	100% O2	1520 - 760	0	2:15

Take away lesson for perfusionists: Reset the oxygen clock and reduce the potential for cardiac oxygen toxicity or reperfusion injury by reducing FiO2 prior to cross clamp removal.

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The toxic effects of high oxygen concentration can be prevented by taking 'air breaks'. Air breaks help the antioxidants 'catch up' in a high oxygen system. For example, during recompression/decompression treatment for decompression sickness (the bends), divers breath pure oxygen for 20 minutes followed by breathing room air for 5 minutes beginning at 3 atmospheres of pressure. The pO2 of pure oxygen at 3 atmospheres is 2280 mmHg. After breathing pure oxygen for 20 minutes, the diver breaths only room air for 5 minutes, which at this pressure has a pO2 of 479. Nonetheless this is enough to restore antioxidant activity to normal. By breathing pure oxygen, the dissolved nitrogen is more rapidly removed from the body as decompression proceeds in stages. Without the use of pure oxygen during decompression, the treatment would take more than 10 times as long to remove the nitrogen from the tissues and blood.

Perfusionists who are concerned with the potential for oxygen toxicity can perform a similar strategy to reduce the number of nitrogen bubbles going into the patient or remove any nitrogen bubbles already in a patient; operating the sweep gas FiO2 at 100% for 20 minutes, followed by an FiO2 of 50% or less for 5 minutes to reset the oxygen clock. An FiO2 of 50% (pO2 = 380 mmHg) is thought to be a safe oxygen level in mammals, without the risk of accumulating oxygen tolerance units and overwhelming the function of the antioxidants. Air breaks can be utilized at specific procedural points such as when the aortic cross clamp is removed or when reperfusion begins after deep hypothermic arrest.

Scenario # 5: Oxygen Toxicity
Off Gassing For A Space Walk To Prevent Nitrogen Emboli

Procedure to off gas nitrogen before a space walk*

1. Reduce cabin pressure from 760 mmHg (sea level = 14.7 psi) to 510 mmHg (Pike's Peak 14,114 ft = 9.9 psi)
2. Pre-breathe 100% O2 for 2 hours
3. Don space suit w/ 100% O2
4. Enter air lock
5. Reduce suit pressure to 207 mmHg (Mt. Everest 29,035 ft = 4 psi)
6. Reduce air lock pressure to 0 mmHg (the vacuum of space = 0 psi)
7. No nitrogen in the tissues to form occlusive bubbles during rapid decompression from 510 to 207 mmHg

Take away lesson for perfusionists: nitrogen can be off gassed during the time span of a routine CPB procedure.

*Horrigan DJ, et al. Extravehicular Activities, in Space Biology & Medicine, A. E. Nicogossian, et al, eds. 1996, American Institute Of Aeronautics And Astronautics, Reston, VA., pp 533-46.
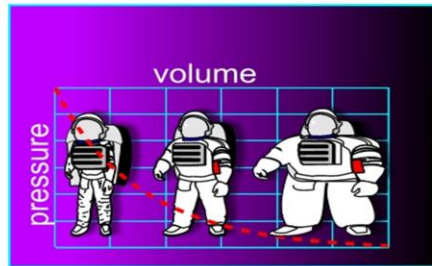
Too much suit pressure in the vacuum of space will balloon the suit and splint the arms and legs so they cannot bend.

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Astronauts face a similar danger during a space walk. It is necessary to reduce the pressure within the space suit from 14.7 psi to only 4 psi when the hatch out into space is opened. The suit pressure must be reduced to this level to prevent ballooning of the suit in the vacuum of space which would make the astronaut unable to bend his/her arms or legs. The only way this can be done is if the astronauts breath pure oxygen for 2 hours prior to donning their space suit. This 'off-gasses' the nitrogen from their tissues. After two hours the astronauts can tolerate the rapid reduction of atmospheric pressure from 14.7 to 4 psi without the formation of lethal nitrogen emboli. Without nitrogen off-gassing, an immediate pressure drop this great would result in crippling or lethal gaseous emboli.

Scenario # 5: Oxygen Toxicity

Neurologic complication comparison:
CPB vs. hyperbaric hyperoxia

- **CNS complications from CPB**
  - **stroke = 1.5% (CABG) to 10% (valves)**
  - **asymptomatic brain infarct (MRI) = 18%**
  - Floyd et al. 2006

- **Hyperbaric hyperoxia CNS event < 0.01%**
  - Neumeister. 2008

- **Hyperoxia on CPB probably does not cause CNS complications from oxygen toxicity in non-hypoxemic patients**

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   Open heart patients are subject to high risks of central nervous system (CNS) complications from cardiopulmonary bypass (CPB), depending on the type of procedure. These complications arise mostly from atherosclerotic, thrombotic and gaseous micro emboli entering the brain rather than oxygen toxicity. Hyperbaric patients are treated with much higher levels of oxygen for comparable periods of time and have few CNS complications.
   Patients on CPB may benefit from using the oxygenator to transform nitrogen bubbles to oxygen bubbles as they exit the pump. Furthermore any nitrogen bubbles already trapped in the cerebral vasculature would be more rapidly removed if hyperoxia were used during CPB.

Scenario # 6: Reperfusion Injury
Definition

- Reperfusion injury occurs when antioxidants are inactivated by ischemic intracellular pH changes, so that any amount of oxygen will produce ROS when reperfusion is established.
  - AOX = antioxidants
  - ROS = reactive oxygen species
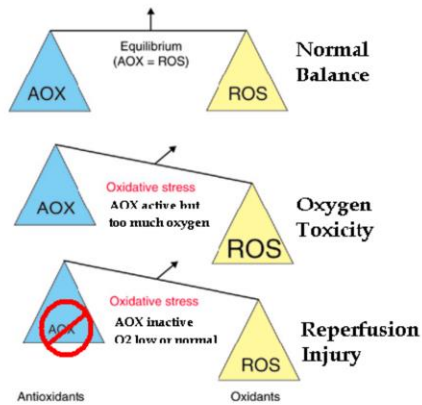
Reperfusion injury occurs after tissues undergo a period of reduced oxygenation caused by poor perfusion. During the ischemic period anaerobic metabolism causes metabolic acids to build up in tissue. Poor perfusion also inhibits the removal of carbon dioxide which builds up in the tissues. The resulting intracellular acidosis deactivates the antioxidants. When perfusion is restored, oxygen and calcium enter the weakened cells and cause reperfusion injury before the intracellular pH can be normalized and the antioxidants reactivated. The oxygen stress injury occurs even when the perfused oxygen levels are low. The use of elevated oxygen levels to reperfuse ischemic tissues can further magnify the damage.

The best way to avoid reperfusion injury is to avoid ischemia. However when this is not possible, such as when the heart is cross clamped or during deep hypothermic arrest, the perfusionist should employ a reperfusion strategy to minimize the damage.

Scenario # 6: Reperfusion Injury
Occurs rapidly with high or low oxygen in ischemic tissues

- "When an organ is deprived of its blood supply it is injured, not just by the temporary loss of oxygen, but also by the ***ROS that are generated by reaction with the oxygen that is reintroduced at reperfusion***, when the blood supply is restored."
    - Bulkley. 2002

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FREE RADICALS AND REACTIVE OXYGEN SPECIES: The evolution of a scientific concept, Gregory Bulkley, 2002, <http://www.cosmos-club.org/web/journals/2002/bulkley.html>

Ischemia/reperfusion injury is a particularly fascinating example of ROS-mediated disease. When an organ is deprived of its blood supply (ischemia) it is injured, not just by the temporary loss of oxygen, but also by the ROS that are generated by reaction with the oxygen that is reintroduced at reperfusion, when the blood supply is restored. In some clinical situations, we can prevent this injury by giving antioxidants, sometimes even after the period of ischemia, but just prior to reperfusion. For example, the preservation of kidneys, livers, and other organs in solutions that contain antioxidants, as well as other agents, is now routine prior to their transplantation. Another example is the use of drugs that block the function of free radical generating enzymes prior to stopping the heart for cardiac surgery. These drugs help prevent reperfusion injury when the heart is restarted and flow is restored. This reperfusion injury mechanism also has been found to play an important role in patients suffering from multiple organ failure after trauma, massive surgery, or shock. Multiple organ failure is now the leading cause of death in intensive care units, and extensive efforts are under way to understand better how ROS contribute to this syndrome."

Ihnken K, Morita K, Buckberg GD, Young HH. Studies of hypoxemic/reoxygenation injury with aortic clamping: XI. Cardiac advantages of normoxemic versus hyperoxemic management during cardiopulmonary bypass. J Thorac Cardiovasc Surg 1995;110:1255-64. "The conventional way to start cardiopulmonary bypass is to prime the cardiopulmonary bypass circuit with hyperoxemic blood (oxygen tension about 400 mm Hg) and deliver cardioplegic solutions at similar oxygen tension levels. This study tests the hypothesis that an initial normoxemic oxygen tension strategy to decrease the oxygen tension-dependent rate of oxygen free radical production will, in concert with normoxemic blood cardioplegia, limit reoxygenation damage and make subsequent hyperoxemia (oxygen tension about 400 mm Hg) safer. Thirty-five immature (3 to 5 kg, 2 to 3 week old) piglets underwent 60 minutes of cardiopulmonary bypass. Eleven control studies at conventional hyperoxemic oxygen tension (about 400 mm Hg) included six piglets that also underwent 30 minutes of blood cardioplegic arrest. Of 25 studies in which piglets were subjected to up to 120 minutes of ventilator hypoxemia (reducing fraction of inspired oxygen to 5% to 7%; oxygen tension about 25 mm Hg), 11 underwent either abrupt (oxygen tension about 400 mm Hg, n = 6) or gradual (increasing oxygen tension from 100 to 400 mm Hg over a 1-hour period, n = 5) reoxygenation without blood cardioplegia. Fourteen others underwent 30 minutes of blood cardioplegic arrest during cardiopulmonary bypass. Of these, nine were reoxygenated at oxygen tension about 400 mm Hg, and five others underwent normoxemic cardiopulmonary bypass and blood cardioplegia (oxygen tension about 100 mm Hg) with systemic oxygen tension raised to 400 mm Hg after aortic unclamping. Measurements of lipid peroxidation (conjugated dienes and antioxidant reserve capacity) and contractile function (pressure-volume loops, conductance catheter, end-systolic elastance) were made before and during hypoxemia and 30 minutes after reoxygenation. <u>Hyperoxemic cardiopulmonary bypass did not produce oxidant damage or reduce functional recovery after cardiopulmonary bypass in nonhypoxemic controls. In contrast, abrupt and gradual reoxygenation without blood cardioplegia produced significant lipid peroxidation (84% increase in conjugated dienes), lowered antioxidant reserve capacity 68% +/- 5%, 44% +/- 8%, respectively, and decreased functional recovery 75% +/- 6% (p < 0.05), 66% +/- 4% (p < 0.05).</u> Similar impairment followed abrupt reoxygenation before blood cardioplegic myocardial management, because conjugated diene production increased 13-fold, antioxidant reserve capacity fell 40%, and contractility recovered only 21% +/- 2% (p < 0.05). Conversely, normoxemic induction of cardiopulmonary bypass and blood cardioplegic myocardial management reduced conjugated diene production 73%, avoided impairment of antioxidant reserve capacity, and resulted in 58% +/- 11% recovery of contractile function."

Summary

1. Hyperoxia changes nitrogen in bubbles to oxygen.

2. Hyperoxia improves tissue hypoxia due to hemodilution.

3. Hyperoxia can counteract metabolic acidosis in shock.

4. Hyperoxia tissue loading extends the safe DHCA time.

5. Hyperoxia causes oxygen toxicity with lengthy exposure (over 5 hours), but can be alleviated with 'air breaks'.

6. Hyperoxia causes reperfusion injury if ischemia/hypoxia is first present.

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REFERENCES 1-14

113

1. Raymond PD, Marsh NA. Alterations to haemostasis following cardiopulmonary bypass and the relationship of these changes to neurocognitive morbidity. Blood Coagul Fibrinolysis. 2001 Dec;12(8):601-18.

2. Floyd TF, Shah PN, Price CC, et al. Clinically Silent Cerebral Ischemic Events After Cardiac Surgery: Their Incidence, Regional Vascular Occurrence, and Procedural Dependence. Ann Thorac Surg 2006; 81(6):2160-2166.

3. Borger MA, Feindel CM. Cerebral emboli during cardiopulmonary bypass: effect of perfusionist interventions and aortic cannulas. J Extra Corpor Technol 2002; 34(1):29-33.

4. Habib RH, Zacharias A, Schwann TA, et al. Adverse effects of low hematocrit during cardiopulmonary bypass in the adult: should current practice be changed? J Thorac Cardiovasc Surg 2003; 125(6):1438-50.

5. Habib, R. H., A. Zacharias, et al. (2005). "Role of hemodilutional anemia and transfusion during cardiopulmonary bypass in renal injury after coronary revascularization: implications on operative outcome." Crit Care Med 33(8): 1749-56.

6. Karkouti, K., W. S. Beattie, et al. (2005). "Hemodilution during cardiopulmonary bypass is an independent risk factor for acute renal failure in adult cardiac surgery." J Thorac Cardiovasc Surg 129(2): 391-400.

7. Ranucci, M., F. Romitti, et al. (2005). "Oxygen delivery during cardiopulmonary bypass and acute renal failure after coronary operations." Ann Thorac Surg 80(6): 2213-20.

8. Habler O, Kleen M, Kemming G, Zwissler B. Hyperoxia in extreme hemodilution. Eur Surg Res 2002; 34(1-2):181-7.

9. Kemming GI, Meisner FG, Kleen M, et al. Hyperoxic ventilation at the critical haematocrit. Resuscitation 2003; 56(3):289-97.

10. Kemming GI, Meisner FG, Meier J, et al. Hyperoxic ventilation at the critical hematocrit: effects on myocardial perfusion and function. Acta Anaesthesiol Scand 2004; 48(8):951-9.

11. Meier J, Kemming G, Meisner F, et al. Hyperoxic ventilation enables hemodilution beyond the critical myocardial hemoglobin concentration. Eur J Med Res 2005; 10(11):462-8.

12. Brasel, K., D. McRitchie, and P. Dellinger, Canadian Association of General Surgeons and American College of Surgeons Evidence Based Reviews in Surgery. 21: the risk of surgical site infection is reduced with perioperative oxygen. Can J Surg, 2007. 50(3): p. 214-6.

13. Dexter F, Kern FH, Hindman BJ, Greeley WJ. The brain uses mostly dissolved oxygen during profoundly hypothermic cardiopulmonary bypass. Ann Thorac Surg 1997; 63(6):1725-9.

14. Nollert G et al. J Thorac Cardiovasc Surg 1999

REFERENCES 15-28

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15. Pearl JM, Thomas DW, Grist G, Duffy JY, Manning PB. Hyperoxia for management of acid-base status during deep hypothermia with circulatory arrest. Ann Thorac Surg 2000 Sep; 70(3):751-5.
16. Bauer V, Bauer F. Reactive oxygen species as mediators of tissue protection and injury. Gen Physiol Biophys 1999; 18 Spec No:7-14.
17. Hyperbaric Oxygen Therapy; Michael Neumeister, MD, FRCSC, FACS, Program Director, Assistant Professor, Department of Surgery, Division of Plastic Surgery, Southern Illinois University School of Medicine, http://www.emedicine.com/plastic/topic526.htm
18. National Oceanic and Atmospheric Administration (NOAA) Diving Manual for Science and Technology, 4th Edition; U.S. Department of Commerce, Technology Administration, National Technical Information Service, Springfield, Virginia 22161
19. U.S Navy Diving Manual, NAVSHIPS 0994-001-9010. Washington, DC: Dept. of the Navy, 1991.
20. Guo S, Counte MA, Romeis JC. Hyperbaric oxygen technology: an overview of its applications, efficacy, and cost-effectiveness. Int J Technol Assess Health Care 2003; 19(2):339-46.
21. Bennett M, Jepson N, Lehm J. Hyperbaric oxygen therapy for acute coronary syndrome. Cochrane Database Syst Rev 2005(2):CD004818.
22. Floyd TF, Shah PN, Price CC, et al. Clinically Silent Cerebral Ischemic Events After Cardiac Surgery: Their Incidence, Regional Vascular Occurrence, and Procedural Dependence. Ann Thorac Surg 2006; 81(6):2160-2166.
23. FREE RADICALS AND REACTIVE OXYGEN SPECIES, GREGORY B. BULKLEY, http://www.cosmos-club.org/web/journals/2002/bulkley.html
24. Becker LB, New concepts in reactive oxygen species and cardiovascular reperfusion physiology. Cardiovascular Research 61 (2004);461-470
25. Ihnken K, Morita K, Buckberg GD, Young HH. Studies of hypoxemic/reoxygenation injury with aortic clamping: XI. Cardiac advantages of normoxemic versus hyperoxemic management during cardiopulmonary bypass. J Thorac Cardiovasc Surg 1995; 110(4 Pt 2):1255-64.
26. KH Polderman, Crit Care Med 2009 37:7(Suppl), S188
27. DeFoe GR, Ross CS, Olmstead EM, et al. Lowest hematocrit on bypass and adverse outcomes associated with coronary artery bypass grafting. Northern New England Cardiovascular Disease Study Group. Ann Thorac Surg 2001;71:769-76.
28. Grist G. Should Perfusionists Use a Transfusion Trigger on Cardiopulmonary Bypass? AmSECT Today, November/December 2009, 12(6): pgs 4-5,13.

Beyond Fick: Discussions On Advanced Perfusion Theory

Session 4: Breaking The Reperfusion Barrier: Perfusion's 21st Century Challenge

Gary Grist RN CCP

No Disclosures

SESSION 4 TABLE OF CONTENTS

OBJECTIVES

1. Describe the mechanisms of reperfusion injury and its relationship to shock and CPR patients.

2. Explain the strategy to revive cardiac arrest patients with the heart/lung pump who are not responsive to CPR resuscitation.

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After a patient undergoes a cardiac arrest followed by CPR, the sudden reperfusion of previously ischemic tissues with warm, oxygenated blood either by the return of the patient's own spontaneous circulation (ROSC) or a heart-lung pump can do more damage than continued ischemia. The resultant reperfusion injury is the barrier that prevents the successful resuscitation of many patients. It is part of a 'Catch 22"* scenario wherein failure at resuscitation automatically results in the patient's death and success at resuscitation triggers a reperfusion injury that can frequently result in significant sequelae that are hardly better than death; the so-called post-resuscitation syndrome. At some indeterminate time during a resuscitation episode the patient passes a point of no return wherein cardiac restart or the use of extracorporeal support will result in a lethal reperfusion injury. The goal is not to determine the actual time of the point of no return, which most likely will be less than 30 minutes. The real goal is to take control of the reperfusion injury potential (RIP) by using a strategy of extracorporeal resuscitation that actively combats reperfusion injury, stops the Catch 22 scenario and breaks the reperfusion barrier. A reperfusion strategy using extracorporeal support can change the fundamental nature of resuscitation medicine for the 21st century.

*The term "Catch-22" describes a problematic situation for which the only solution is denied by a circumstance inherent in the problem. In this case, if resuscitation fails the patient dies. But if resuscitation is successful, the patient still dies as a result of the reperfusion injury caused by the return of capillary perfusion. "Catch-22" is the title of a novel by the American author Joseph Heller who first coined the term.

FOUR MECHANISMS OF REPERFUSION INJURY

- Oxidative stress √
- Calcium Stress √
- Neutrophil-Endothelium Interaction
- Apoptosis

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There are four primary mechanisms that combine to manifest reperfusion injury:
1. oxidative stress
2. calcium stress
3. the neutorphil-endothelium interaction
4. apoptosis.
If 1 and 2 can be controlled then 3 and 4 will be minimized.

OXYGEN TOXICITY VS. REPERFUSION INJURY

- AOX = antioxidants

- ROS = reactive oxygen species

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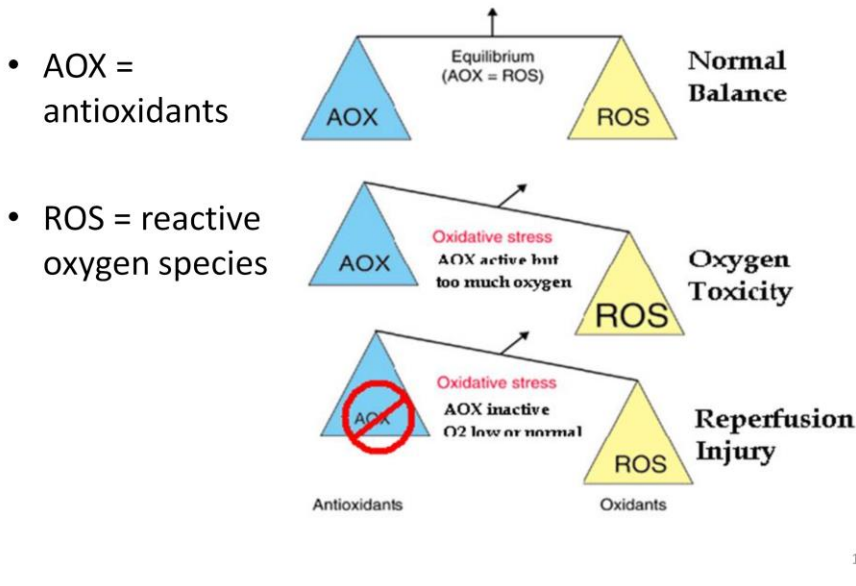
   Oxygen is a highly reactive molecule; it rots rubber, rusts iron, supports combustion and, in biological systems, is the source of reactive oxygen species (ROS). The most common of these include peroxides, superoxides, hypochlorous acid and hydroxyl radicals. Small amounts of these substances are needed for specific cellular process. However too many can result is significant cell damage because they contain unpaired electrons that can alter normal cell metabolism.

   Antioxidants (AOX) are biological firemen that control the production of ROS. The most common include peroxidases, superoxide dismutase, catalase and glutathione. Vitamins such as C & E are coenzymes that aid AOX in their function. Many of the AOX are enzymes that function best when the pH remains within normal physiologic limits (pH > 7.20). Normally ROS production is balanced by AOX function. However ROS can accumulate when the amount of oxygen entering the organism exceeds the functional capacity of the AOX. This is known as oxygen toxicity. Oxygen toxicity occurs even though the AOX are functioning normally and tissue perfusion is unimpaired. It usually requires many hours or days to develop. A common medical situation involving oxygen toxicity is the extended use of high levels of oxygen on the airway and lung tissues. Typically breathing 100% for more than 7 days will result in significant lung damage from oxygen toxicity.

   On the other hand, reperfusion injury occurs only after a period of ischemia caused by poor perfusion or hypoxia during which time tissues become anoxic and acidotic. The acidosis stops the normal function of AOX. This is followed by the sudden reintroduction of oxygen when normal perfusion is reestablished. Until normal intracellular pH is restored ROS production is uncontrolled, resulting in significant tissue damage. Unlike oxygen toxicity, the level of oxygen needed to cause damage is not great and the damage occurs immediately upon reperfusion and continues to evolve until normal intracellular pH is restored. The restoration of normal intracellular pH can take many hours, depending on the magnitude of the acidosis, during which time the ROS continue to cause damage.

ANTIOXIDANTS

- Catalase, superoxide dismutase, glutathione peroxidase, etc.

- Protect against oxygen's damaging effects
    - One catalase molecule neutralizes 40 million hydrogen peroxide molecules every second
        - CAT + 2H2O2 > 2H2O + O2 + CAT

- pH sensitive: > 7.20
- Activity slowed with hypothermia

Many different types of AOX are needed to deal with the many types of ROS. Each AOX is uniquely suited to neutralize the toxic effects of specific ROS. For example, one catalase molecule can neutralize 40,000,000 hydrogen peroxide molecules every second. However if the pH falls below 7.2 the effectiveness of the enzyme is greatly reduced. Enzymatic function is also reduced during hypothermia.

COMPLICATIONS VS. REPERFUSION INJURY

COMPLICATIONS
OF EXTRACORPOREAL SUPPORT PATIENTS

- Brain damage
  - encephalopathy
  - coma
  - seizure
  - infarct
  - hemorrhage
- Cardiac failure
  - arrhythmia
  - ventricular failure
  - cardiac stun
  - stone heart
  - elevated cardiac enzymes
- Multiple organ failure
  - renal failure
  - pulmonary infiltrates/hemorrhage
  - elevated liver enzymes
  - elevated glucose
  - gut ulcer/slough
  - coagulopathy
- Systemic inflammatory response
- Failure to improve

SYMPTOMS OF
REPERFUSION INJURY

- Brain damage
  - encephalopathy
  - coma
  - seizure
  - infarct
  - hemorrhage
- Cardiac failure
  - arrhythmia
  - ventricular failure
  - cardiac stun
  - stone heart
  - elevated cardiac enzymes
- Multiple organ failure
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  - elevated glucose
  - gut ulcer/slough
  - coagulopathy
- Systemic inflammatory response
- Failure to improve

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Patients undergoing mechanical cardiopulmonary support do not normally expire from their primary disease. In respiratory patients, for example, infants on ECMO for meconium aspiration syndrome or primary pulmonary hypertension do not usually die from these conditions. Rather they suffer a lethal complication such as a cerebral hemorrhage or multiple organ failure. Adults on mechanical support for acute (adult) respiratory distress syndrome (ARDS) or pneumonia frequently expire from a stroke (brain infarction or hemorrahge) or simply failure to improve. Cardiac patients frequently go into multiple organ failure while waiting for the heart to recover or develop systemic inflammatory response with all its accompanying pathologies.

There is general acceptance that early intervention with mechanical support relates to improved survival. For example, surviving neonates with respiratory disease are placed on ECMO an average of 2 days after birth while non-survivors are placed on ECMO an average of 4 days after birth. However no one has really determined when it is futile to initiate mechanical support. This is usually determined retrospectively; i.e. if a fatal complication occurs the patient was probably put on mechanical support "too late"(1,2).

The real cause of these complications is the implementation of mechanical support itself (which is intended to save the patient) during the time when the patient is most susceptible to reperfusion injury. The list of extracorporeal support complications are the same types of things that would be expected from reperfusion injury.

1. Grist G, Whittaker C, Merrigan K, Fenton J, Pallotto E, Lofland G. Defining the late implementation of extracorporeal membrane oxygenation (ECMO) by identifying increased mortality risk using specific physiologic cut-points in neonatal and pediatric respiratory patients. J Extra Corpor Technol 2009;41:213-9

2. Grist G, Whittaker C, Merrigan K, et al. Identifying neonatal and pediatric cardiac and congenital diaphragmatic hernia extracorporeal membrane oxygenation patients at increased mortality risk. J Extra Corpor Technol;42:183-90.

OXYGEN STRESS REPERFUSION INJURY
Myocyte Cell Death By Ischemic Anoxia And Subsequent Reperfusion (Reoxygenation)
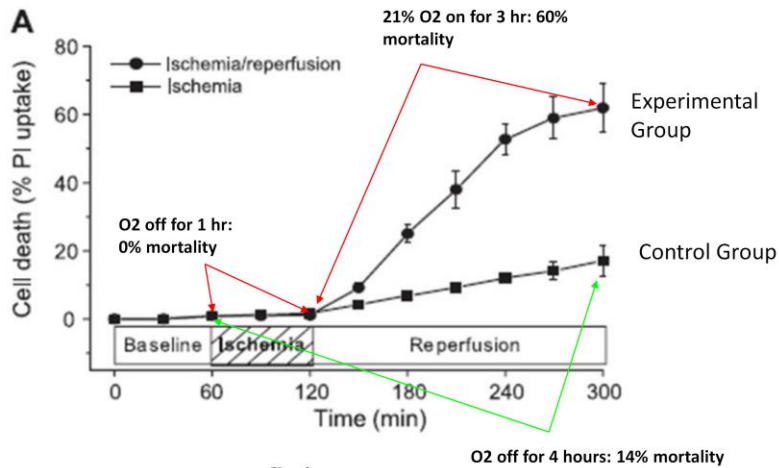
Post coronary balloon angioplasty infarcts
X-Clamp w/ hypothermia
Becker. 2004

   This experiment* illustrates the impact that oxygen has on hypoxic/ischemic cells. As a control group, a culture of chicken cardiac myocytes was subjected to four hours of simulated ischemia by removing oxygen from the culture environment. At the end of one hour very few of the cells had expired. At the end of four hours 14% of the cells had expired. The experimental group was exposed to only one hour of simulated ischemia after which 21% oxygen was reintroduced to the culture environment. Over the next three hours of simulated reperfusion, 60% of the cells expired. Why was the experimental group mortality rate so much higher than the control group? During the one hour simulated ischemia, the experimental group cells entered into anaerobic metabolism. This produced metabolic acids and changed the internal pH of the cells which deactivated the antioxidants. When oxygen was reintroduced after only one hour, reactive oxygen species destroyed vital cellular components resulting in the death of the cells. No oxygen was re-introduced into the control group. So even after four hours of anoxia very few cells died.
   This experiment demonstrates the lethality of oxygen stress and suggests that cells may benefit from continued ischemia until the intracellular pH can be corrected and the antioxidants reactivated. This further suggests that hypoxic/ischemic patients who are mechanically reperfused without first correcting intracellular pH and reactivating the antioxidants will be subjected to the extreme morbidity of reperfusion injury.
   The use of balloon angioplasty (percutaneous transluminal coronary angioplasty, PTCA) is usually very successful in opening obstructed coronary arteries. Occasionally the patient will suffer a post-PTCA cardiac infarction. The assumption is often made that coronary re-stenosis (even after stent placement) is responsible. However an alternate explanation is just as plausible; that the infarction is caused by the reperfusion of hypoxic/ischemic cells after the coronary artery is opened, as this experiment simulates. This reperfusion damage is avoided during cardiac cross clamping by the use of hypothermia.
   *Becker LB. New concepts in reactive oxygen species and cardiovascular reperfusion physiology. Cardiovasc Res 2004;61:461-70.
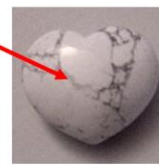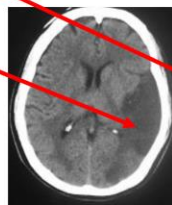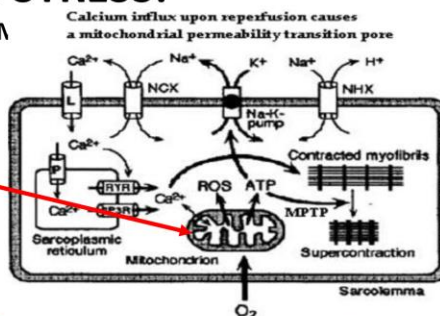
CALCIUM STRESS:

The second major mechanism of reperfusion injury is calcium stress. This is also called a paradox because living systems need calcium for normal cellular processes. But the uncontrolled influx of calcium into the cell or release of calcium from intracellular storage sites (such as the sarcoplasmic reticulum) after ischemia results in mitochondrial damage called a 'mitochondrial permeability transition pore' or MPTP*. This occurs in excitable cells such as cardiac conduction cells, cardiac myocytes and neurons.

The MPTP causes mitochondrial membrane swelling and the uncontrolled release of ATP from the mitochondria. In cardiac myocytes, this causes normally contacting myofibrils to super contact and not relax. Over time, as more and more myofibrils super contact, the heart becomes stiffer and less efficient at pumping. During CPR resuscitation the efficiency of chest compressions is reduced as the heart stiffens. More preload is needed and more robust compressions are required to maintain the same systemic perfusion. A fibrillation feedback condition also develops wherein increasing energy (Joules) is needed for defibrillation each time the heart fibrillates until a point is reached when the heart will not respond to defibrillation.
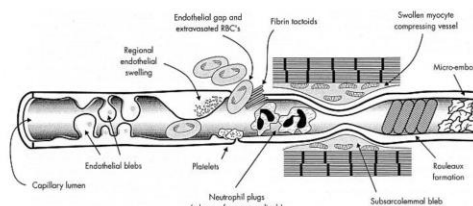
The reversible form of this cardiac myocyte hypercontracture is known as 'cardiac stun'. Hypercontracture can progress to the point where the cardiac contracture/relaxation cycle is very poor and the heart muscle irreversibly damaged; a condition known as 'stone heart'.

The MPTP effect can be particularly damaging to the central nervous system (CNS). In the typical ECMO patient with right neck venoarterial cannulation, the CNS damage by infarction occurs most often in the left brain. At first, this seems illogical because the right brain's blood supply is greatly diminished by the ligation of the right carotid artery. However once the patient is placed on ECMO, the left carotid will immediately carry warm, well oxygenated blood directly to the left brain. If reperfusion injury potential is present in the brain, significant left sided CNS damage will occur. The right brain, although deprived of much of its circulation, is more or less protected from sudden reperfusion from the ECMO pump. Blood gradually enters the right brain from the right vertebral artery and circle of Willis after first passing through other parts of the body and mixing with non-ECMO blood. This reduces the oxygen and calcium levels before the blood enters the right brain. The incidence of left brain infarctions is almost 6 times greater than right brain infarctions, even though the right carotid is ligated prior to ECMO.

*Halestrap AP. Calcium, mitochondria and reperfusion injury: a pore way to die. Biochem Soc Trans 2006;34:232-7.
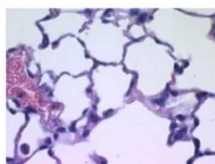
NEUTROPHIL-ENDOTHELIUM INTERACTION

- Neutrophils, activated by ischemia, release cytotoxic granules and ROS, damaging capillaries.

- Damaged capillaries become a blood flow "obstacle course".

- *No reflow* phenomenon is caused by cellular aggregation in the damaged capillaries. This is commonly diagnosed as disseminated intravascular coagulation (DIC) systemically or ARDS w/ Diffuse Alveolar Damage (DAD) in the lungs
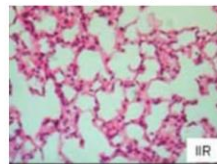
http://www.benbest.com/cryonics/ischemia.html#reperfuse

Normal mouse lung

Mouse lung after gastric ischemic/hypoxia reperfusion

http://www.thoracic.org/sections/clinical-information/critical-care/critical-care-research/animal-models-of-acute-lung-injury.html

Neutrophils are activated during reperfusion, releasing cytotoxic granules and ROS. They can do significant damage to the capillary endothelium inside of the ischemic areas. In other non-ischemic areas such as the lungs, capillaries are subject to further attack by activated neutrophils. In an experiment by Mura et al, mice were subjected to gut ischemia by clamping of the gastric artery for 30 minutes after which reperfusion of the gut was allowed. Soon after gut reperfusion, the pulmonary capillaries became congested with activated neutrophils, damaging the lungs and severely compromising pulmonary function. This occurred even though the lungs themselves were not directly exposed to ischemia.

This is a form of ARDS which is the most common cause of death in the ICU, responsible for 50% of the mortalities. ARDS is usually associated with a 'trigger' such as trauma, burns, aspiration, blood transfusions, drug over dose, acute Illness (cardiac arrest), pneumonia, sepsis, pancreatitis and many other conditions. However the common denominator associated with all of these things is shock. Patients in shock have under perfused capillaries and tissues which become hypoxic/ischemic. When these capillaries are suddenly reperfused during resuscitation, reperfusion injury is quickly manifested and often results in diffuse alveolar damage (DAD) and bilateral infiltrates in the lung (ARDS). The lesser form is called acute lung injury (ALI).

Besides damaging the capillaries, the neutrophils aggregate in vital areas, further damaging tissues and inhibiting normal perfusion. Capillaries damaged by reperfusion injury become an obstacle course to the smooth passage of red blood cells. Damage can include endothelial blebs, endothelial swelling, rupture, fibrin tactoids, activated platelets, swollen myocytes, subsarcolemmal blebs, rouleaux formation, and, of course, activated neutrophils. After the successful resuscitation and resolution of shock, this 'no reflow' phenomenon can result in a second round of localized ischemia and severely compromise perfusion of the organ systems. This is commonly diagnosed as disseminated intravascular coagulation (DIC) systemically and ARDS in the lungs. Externally this may appear as poor perfusion of the extremities with fingers and toes often turning purple and black from the blocked circulation.

Internally the effect can cause organ failure, and brain infarction and/or hemorrhage. Pulmonary hemorrhage after CPR followed by ECPR is a common complication. These hemorrhages are probably precipitated by activated neutrophils and subsequent no reflow

phenomenon.

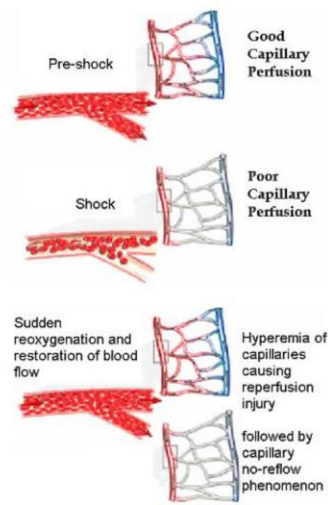ACCELERATED APOPTOSIS CAUSED BY REPERFUSION INJURY
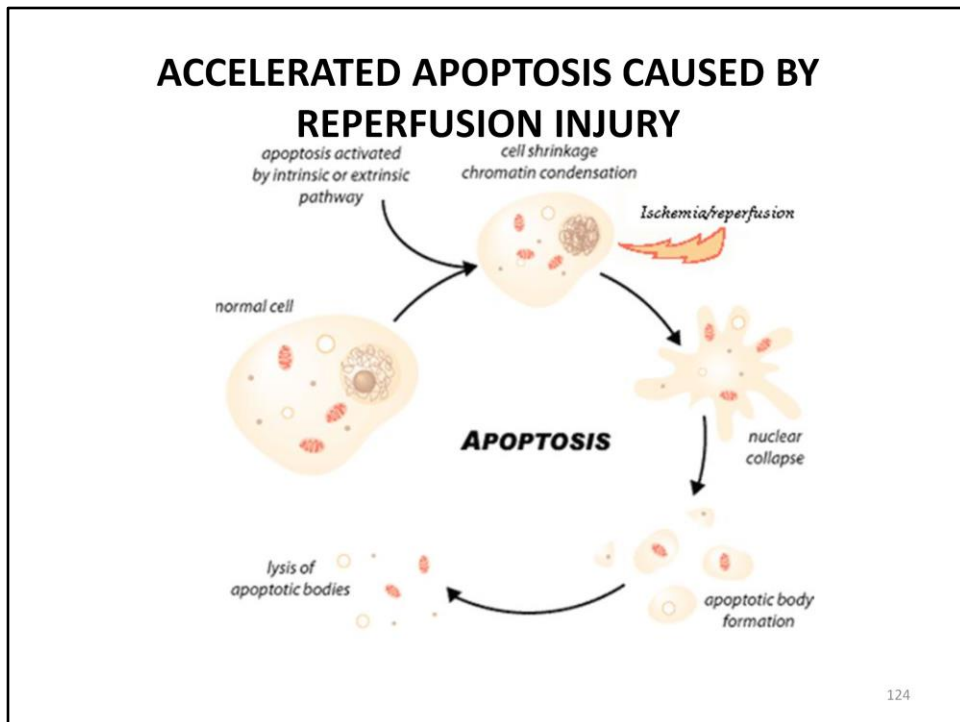
The fourth mechanism of reperfusion injury is accelerated apoptosis, also known as programmed cell death. Apoptosis is the normal process that occurs at the cell's end of life. Normally it is activated by some intrinsic or extrinsic pathway and follows a process of cell shrinkage, nuclear collapse, lysis and finally absorption. However ischemic/reperfusion can jump start apoptosis much earlier causing many otherwise young and normal cells to expire before their time. This can lead to significant organ dysfunction.

REPERFUSION INJURY POTENTIAL (RIP)
Acronym for "Rest In Peace"

- RIP: the hidden risk of a lethal reperfusion injury upon sudden reperfusion of ischemic tissues.

- Shock: inadequate blood flow = poor tissue oxygenation & CO2 removal
  - Cardiogenic
  - Septic
  - Traumatic
  - Hypovolemic
  - Neurogenic

- Shock: a state of insufficient perfusion that holds the potential for reperfusion injury if normothermic oxygenation is suddenly restored.

- RIP markers to assess degree of shock:
  - Tissue anoxia = ↑ corrected anion gap
  - Tissue CO2 retention = ↑ $p[v-a]CO_2$

Pre-shock — Good Capillary Perfusion

Shock — Poor Capillary Perfusion

Sudden reoxygenation and restoration of blood flow — Hyperemia of capillaries causing reperfusion injury — followed by capillary no-reflow phenomenon
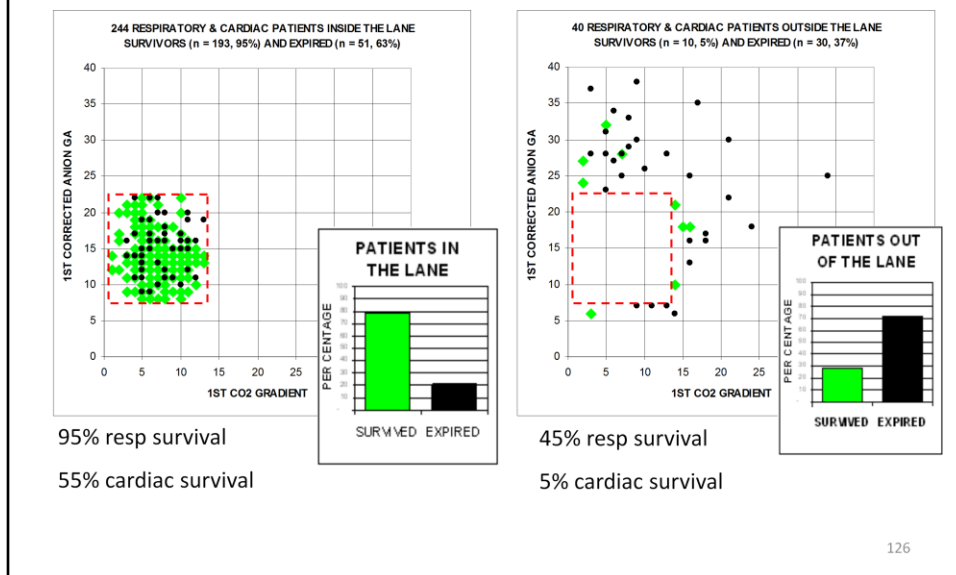
A cause of acute organ failure in transplants.

Reperfusion injury potential (RIP) is the hidden risk of a lethal reperfusion injury upon the sudden reoxygenation of ischemic or anoxic tissues. RIP is most common in patients with shock. Shock is an extended state of insufficient perfusion that holds the potential for reperfusion injury if normothermic reoxygenation is suddenly implemented. There are various types of shock, but typically patients who are in acute hemodynamic failure, patients undergoing resuscitation and CPR, patients with severe acidosis requiring frequent sodium bicarbonate or other buffer base infusions, patients with an elevated anion gap or lactate and patients with a large (>15 mmHg) venoarterial CO2 gradient are at risk for RIP. Hypoxemia is not necessarily a predictor of RIP. The corrected anion gap (AGc) and the venoarterial CO2 gradient are two markers that when combined can quantify the degree of RIP that the patient is experiencing.

In the pre-shock state capillary perfusion is good. During shock capillary perfusion is insufficient and the tissues become acidotic. The acidosis deactivates the antioxidants and weakens the cell membrane potential allowing calcium influx. Upon the sudden reoxygenation and restoration of blood flow, capillary hyperemia occurs causing immediate oxygen stress and calcium stress followed by capillary no-reflow phenomenon and cellular apoptosis.

This is a frequent cause of acute organ failure in transplants. Even though the donor organs are protected by hypothermia during preservation and storage, ischemic acidosis still slowly occurs. During this time RIP develops in the cold donor organ. Re-implantation of the cold, acidotic donor organ into a warm recipient is followed by the sudden reinstitution of perfusion when the surgeon connects the arteries and veins. If RIP is present in the donor organ, reperfusion injury will cause acute and sometimes irreversible organ damage.

RIP is also an acronym for 'Rest In Peace', a common obituary blessing. This is very appropriate because patients with reperfusion injury potential are at a very high risk of dying.

REPERFUSION INJURY POTENTIAL (RIP) MAPPING:
BLOOD PRIMED, NORMOTHERIC ECMO PATIENTS
(N = 284)

244 RESPIRATORY & CARDIAC PATIENTS INSIDE THE LANE
SURVIVORS (n = 193, 95%) AND EXPIRED (n = 51, 63%)

40 RESPIRATORY & CARDIAC PATIENTS OUTSIDE THE LANE
SURVIVORS (n = 10, 5%) AND EXPIRED (n = 30, 37%)

95% resp survival
55% cardiac survival

45% resp survival
5% cardiac survival

The level of shock that a patient is enduring can be determined using the Viability Index (VI). The VI is calculated by adding the corrected anion gap and the venoarterial CO2 gradient together. The high VI scores correlate to a high the level of shock. This, in turn, relates to a high level of RIP. The VI can be charted on a grid (see the charts above). These charts contain the first VI score just after patients were placed on traditional, blood primed, normothermic ECMO.

The patient population was pediatric with most patients weighing less than 10 kg. The diagnoses varied in 2 broad categories; respiratory and cardiac. The respiratory diagnoses included all the traditional neonatal ECMO conditions (with the exception of congenital diaphragmatic hernia); meconium aspiration, primary pulmonary hypertension, respiratory distress syndrome and sepsis. In older patients, diagnoses included primarily pneumonia, respiratory syncytial virus, sepsis and trauma. The most common cardiac diagnoses included pre and post surgery for congenital heart disease and cardiomyopathy.

The VI scores of 95% of the survivors fall into a relatively small area between the corrected anion gaps of 7 and 22 mEq/L and the venoarterial CO2 gradients of 1 and 13 mmHg. This small area is known as the "lane" in reference to the rectangular area beneath a basketball goal from which a player is most likely to make a goal. In contrast, only 61% of the expired patients' VI scores are located in the lane. The overall mortality for patients in the lane is 21%.

Only 5% of the survivors are located outside the lane along with 39% of the expired patients. The patients outside the lane have a mortality rate of 73%. This mortality rate is 3.5 times higher than for patients in the lane. Why such a difference? The VI scores indicate that the patients outside the lane are at a higher level of shock than patients in the lane, therefore they have more RIP. When these patients are placed on ECMO using a blood prime (normal hematocrit levels) and normothermia, the sudden reperfusion of previously ischemic tissues results in reperfusion injury. This can manifest itself in many ways; brain hemorrhage or infarction, pulmonary hemorrhage, cardiac stun, renal failure, multiple organ failure or, simply failure to improve or heal from the original underlying pathology.

Not all patients needing ECMO support have RIP. Indeed hypoxic neonates tend to be resistant to RIP which is probably why neonatal ECMO has been so successful. However older patients with non-neonatal diagnoses are less resistant to RIP and have much poorer survival when placed on ECMO. In many of these patients the use of ECMO has the potential to cause a lethal reperfusion injury which ,in addition to the risk of the underlying disease, adds greatly to the risk of death.

EXTRACOPOREAL SUPPORT STRATEGY FOR ARREST PATIENTS
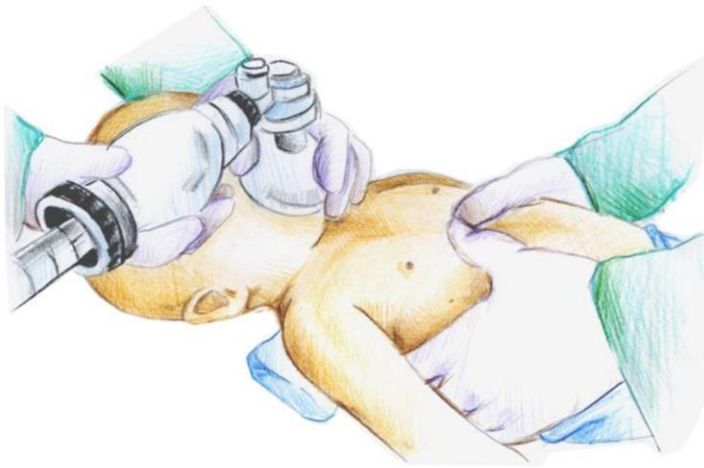
www.aic.cuhk.edu.hk/web8/toc.htm

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   As explained earlier, the institution of normal hematocrit, normal temperature ECMO in a patient with RIP can greatly increase the risk of death. Without a VI score, it is difficult to determine which patients have RIP and to what degree, since all of these patients need extracorporeal support. If it is determined that a patient has RIP, some strategy besides traditional ECMO needs to be employed to address the ramifications of RIP.

   One type of patient who most certainly has RIP is the coding or near code patient. This patient is almost always outside the lane before ECMO can be initiated because RIP develops within a very few minutes due to poor perfusion from CPR. A strategy called ECPR (extracorporeal cardiopulmonary resuscitation) can be utilized in these patients to address each of the four reperfusion injury mechanisms.
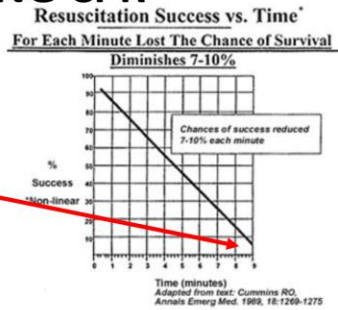
   The terminology for this type of extracorporeal support is by no means standardized. It has also been called emergent ECMO (E-ECMO), rapid deployment ECMO (RD-ECMO) and extracorporeal (or emergent) cardiopulmonary support (ECPS). These terms merely denote the rapid implementation of a pump-oxygenator to support a dying patient. However for this presentation, ECMO will mean the initiation of traditional normal hematocrit, normal temperature extracorporeal support and ECPR will mean the initiation of a strategy of extracorporeal support using hypothermic hemodilution and hypocalcemia to prevent reperfusion injury.

   The typical resuscitation of a patient in severe shock or who has already had a cardiac arrest centers on the goal directed therapy of normalizing cardiac output, blood pressure, arterial oxygen saturation, arterial blood pH, etc. However attempting to resuscitate a patient in this manner without an understanding of the ramifications of reperfusion injury is like treating an infection without knowing anything about bacteria. The results will be 'hit and miss'.
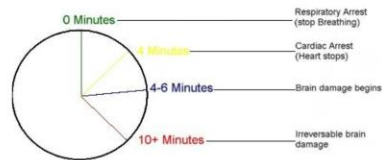
TERMINATING CPR

- 1959
  - Dr. Safar starts CPR
  - 10 minute limit
- 1989
  - 30 years since CPR started
  - Still a 10 minute limit
- 2005 AHA Guidelines for CPR
  - 46 years since CPR started
  - No change in 10 minute limit
    - "For the newborn infant, discontinuation of resuscitation can be justified after 10 minutes without signs of life despite continuous and adequate resuscitative efforts."
- 2008 Current PALS Recommendation
  - 49 years since CPR started
  - 15-30 minute limit
    - Discontinue CPR efforts after 15 minutes for newborn in delivery room. All others, discontinue CPR efforts after 30 minutes if no signs of life.

Resuscitation Success vs. Time*
For Each Minute Lost The Chance of Survival Diminishes 7-10%

Chances of success reduced 7-10% each minute

% Success *Non-linear

Time (minutes)
Adapted from text: Cummins RO, Annals Emerg Med. 1989; 18:1269-1275

Timeframe of a Cardiac Arrest

0 Minutes — Respiratory Arrest (stop Breathing)
4 Minutes — Cardiac Arrest (Heart stops)
4-6 Minutes — Brain damage begins
10+ Minutes — Irreversible brain damage

www.castorcanada.com/chainofsurvival.htm   128

The success of modern CPR resuscitation has not significantly improved since its inception in 1959 at Johns Hopkins University. Even after 30 years of experience, survival for patients undergoing in-house CPR for more than ten minutes was very poor in 1989. In 2005 (46 years after the initiation of CPR), the American Heart Association (AHA) resuscitation recommendation*
 for newborns is to discontinue CPR in 10 minutes if there are no signs of life. Pediatric Advanced Life Support (PALS) currently recommends discontinuing CPR efforts after 15 minutes in newborns and 30 minutes in all others. Successful CPR resuscitation lasting longer than 15 minutes still has a very poor outcome despite 50 years of experience.
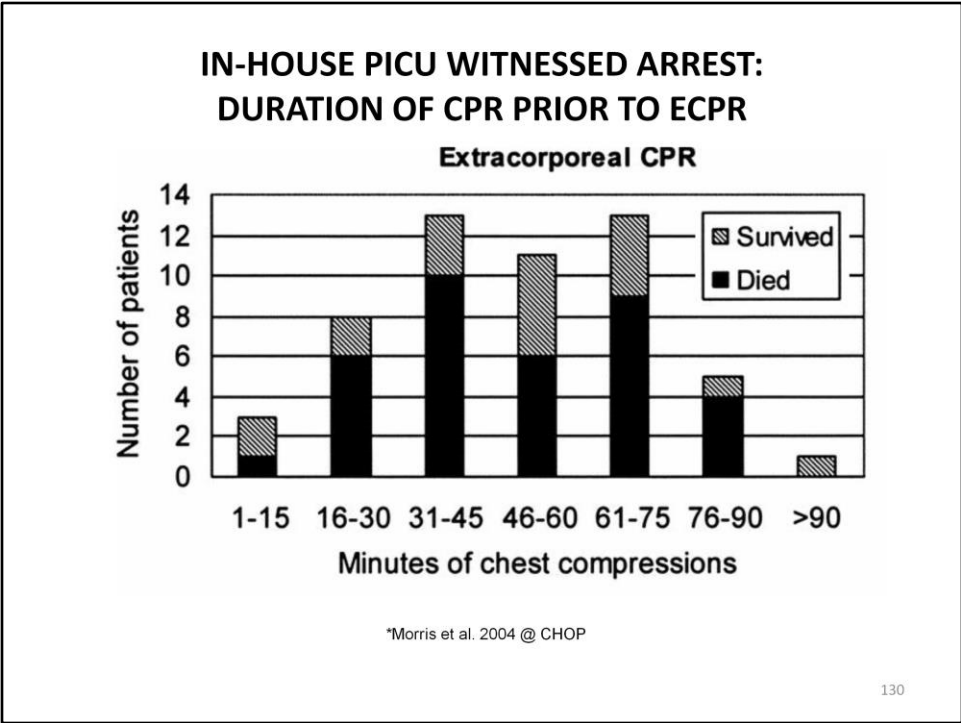
Unless the heart can be restarted within ten minutes, the thinking is that brain damage becomes irreversible and that effective chest compressions, even when started early after cardiac arrest, cannot supply enough oxygen to the brain, heart and other organs to prevent their death from anoxia for more than 30 minutes.

*2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2005;112:IV1-203.

IN-HOUSE PICU WITNESSED ARREST: DURATION OF CPR

Conventional CPR

*Morris et al. 2004 @ CHOP

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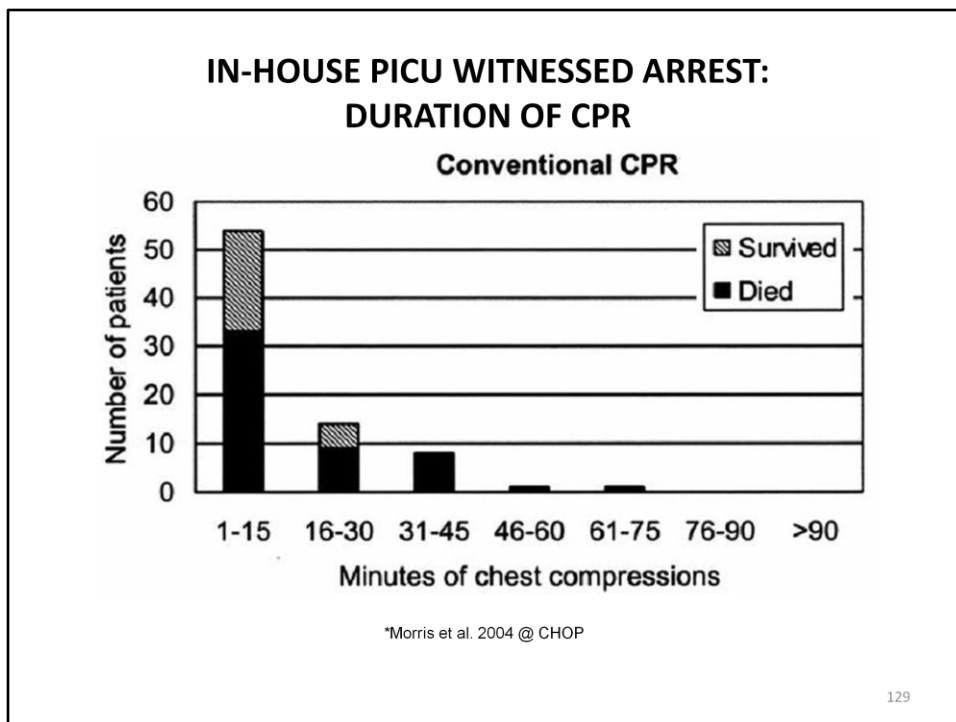
If return of spontaneous circulation (ROSC) does not occur after 30 minutes of advanced cardiac life support (ACLS) interventions including CPR, the patient will not likely recover even if the resuscitation time is extended. A retrospective review of in-hospital ACLS/CPR by Morris at the Children's Hospital of Philadelphia showed that the average CPR time was 8 minutes with 70% of the patients having ROSC. Of these 70%, only about half survived to discharge. No patients receiving ACLS/CPR for longer than 30 minutes survived. Very few patients received ACLS/CPR for longer than 30 minutes, a reflection of AHA and PALS recommendations.

The problem remains that survival occurs in only about 1/3 of in-house ACLS/CPR patients. It is unknown how many patients would have succumbed to their underlying pathology if ACLS/CPR resuscitation was not a factor. However there is a great possibility that some of the deaths were attributable to reperfusion injury that occurred upon ROSC.

**IN-HOUSE PICU WITNESSED ARREST:
DURATION OF CPR PRIOR TO ECPR**

Extracorporeal CPR

*Morris et al. 2004 @ CHOP

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Once ECPR was routinely instituted at the Children's Hospital of Philadelphia , patients were rarely placed on pump in less than 30 minutes and often as long as 90 minutes after cardiac arrest. Survival in these cases was better than ACLS/CPR. The survival rate was unrelated to the duration of CPR.

Post-resuscitation Syndrome

- Fatal outcome after successful resuscitation
  - Mitochondrial damage
    - Cardiac arrythmias and decreased contractility
    - CNS dysfunction and coma
  - No reflow phenomenon
    - Vascular obstruction > microvascular embolism
    - Increased SVR, PVR
    - DIC
    - Multi-organ failure

Post-resuscitation syndrome often occurs after a successful CPR resuscitation and includes pathology that was not present prior to the need for CPR resuscitation. It is characterized by cardiac arrhythmias, decreased cardiac contractility, and CNS dysfunction. These are probably caused by mitochondrial damage. Also commonly seen is vascular obstruction, micro embolism, intravascular coagulation, altered hemodynamics and multiple organ failure. These are probably caused by no reflow phenomenon.

QUESTIONING ACCEPTED DOGMA

- How do we know that brain damage occurs after 10 minutes of cardiac arrest?
  - Answer: Because a few patients are revived after lengthy CPR and have obvious brain damage.
    - Schneider. 1981

- Why should efforts cease after 30 minutes of CPR?
  - Answer: The current concept is that during CPR, poor blood flow kills the brain cells. CNS survival after 30 minutes is unlikely.
    - AHA. 2005
    - AHA. 2006

- New Concept: During CPR, brain cells do not die until the ROSC (or starting ECMO). Sudden tissue reperfusion with warm, oxygenated blood causes reperfusion injury that kills the brain.
   - Idris et al. 2005
    - Becker. 2004

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But what evidence is there that brain damage occurs after 10 minutes of cardiac arrest? And why should efforts cease after 30 minutes of resuscitation CPR? The answer is that a few patients are revived after lengthy CPR and have obvious brain and cardiac damage; also known as post-resuscitation syndrome.

The current concept is that during CPR there is insufficient blood flow and poor oxygen delivery to keep the brain and heart alive. CNS survival, in particular, is very unlikely after 30 minutes. This thinking reflects the AHA and PALS recommendations.

However a new concept suggests that the brain and heart cells do not die during resuscitation CPR until the return of spontaneous circulation (or the implementation of ECMO). At that time, the sudden reperfusion with warm, oxygenated blood results in a reperfusion injury that ultimately kills the brain and heart cells.

RIP MAPPING THE CPR PATIENT

Blood gas values taken from CLINICAL APPLICATION OF BLOOD GASES, FOURTH ED. © 1989, SHAPIRO, HARRISON, CASE & KOZLOWSKI-TEMPLIN, EDs., PP 337-338

REPERFUSION INJURY POTENTIAL MAP

TIME	FiO2	BLOOD GAS TYPE pH / pCO2 / pO2 / base	Δ pCO2
60 min prior to arrest.	30%	ABG 7.37 / 42 / 80 / -1	8
		VBG 7.33 / 50 / 32 / -1	
CPR 5 min	100%	ABG 7.52 / 28 / 436 / -1	30
		VBG 7.31 / 58 / 25 / -2	
CPR 15 min	100%	ABG 7.27 / 48 / 430 / -6	36
		VBG 7.09 / 84 / 25 / -6	
CPR 35 min	100%	ABG 7.11 / 38 / 322 / -19	58
		VBG 6.82 / 96 / 20 / -20	
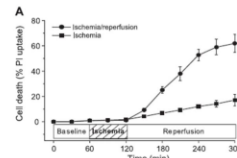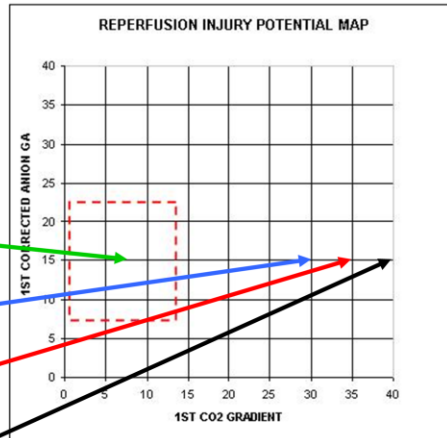
Typically patients undergoing resuscitation CPR will experience a great increase in their venoarterial CO2 gradient. This is caused by a slowing of the blood flow thru the capillaries and the resultant 'backing up' of CO2 in the tissues. In order to make this measurement, an ABG and a central VBG need to be drawn at the same time. The real-life example illustrated above shows the typical pattern seen in a patient undergoing resuscitation CPR for 35 minutes.

The first set of blood gases prior to arrest shows the patient with normal oxygen and CO2 levels, normal pH and base balance. The venoarterial CO2 gradient of 8 mmHg, located in the midpoint of the lane, correlates to a tissue pCO2 of 74 mmHg.

Formula paCO2 + (4 X p[v-a]CO2): 42 + (4 X 8) = 74 mmHg tissue pCO2.

Five minutes after resuscitation CPR is started, the CO2 gradient climbs to 30 mmHg (almost 4 times normal). This plots well outside of the lane and demonstrates that even early in the resuscitation period the patient is developing RIP. Under poor perfusion conditions such as this, the tissue pCO2 increases more than the gradient increase. In other words, a rise in the gradient from 8 to 30 mmHg (a 22mmHg increase) causes a rise in the tissue pCO2 from 74 mmHg to 148 mmHg (a 74 mmHg increase). Notice how the paCO2 appears hypocapnic while the pvCO2 is hypercapnic.

After 15 minutes of CPR, the CO2 gradient is 38 mmHg, relating to a tissue pCO2 of about 192 mmHg.

After 35 minutes of CPR, the CO2 gradient is 58 mmHg relating to a tissue pCO2 of about 270 mmHg.

The large increases in tissue CO2 correlate with intracellular acidosis which is a precondition for RIP. It is not necessary to actually make these ABG & VBG measurements to determine if RIP is developing in a resuscitation CPR patient. The increase in the venoarterial CO2 gradient is an inevitable consequence of CPR, so that after 10-15 minutes all patients will be out of the lane and subject to RIP. If the decision is made to place a patient like this on an ECMO pump, a reperfusion strategy should be used to prevent the lethal reperfusion injury that will occur upon the initiation of extracorporeal support. In addition, since the accumulation of tissue CO2 can be quite large, the risk of reperfusion injury will last until the CO2 gradient can be brought within the lane. This could take many hours.

As previously described the sudden reintroduction of oxygen into anoxic cells can be more deadly than allowing the anoxia to continue while a strategy is formulated to prevent the reperfusion injury form occurring. While not plotted on this example, the anion gap (and even the lactate) may or may not remain within acceptable limits during this relatively short resuscitation time frame.

ECMO VS ECPR STRATEGY

1. ECMO: maintain norm physiology
   - Urgent
     - Patient is "in the lane"
     - Patient not coding
   - Normothermia
   - Blood Prime
     - No hemodilution
   - Normalize iCa

2. ECPR: thwart a lethal physiology
   - Emergent
     - Patient is "out of the lane"
     - Patient coding/ near code
   - Hypothermia
   - Clear prime
     - Intentional hemodilution
   - Reduce iCa
   - Dantrolene

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ECMO should be used to maintain a patient's normal physiology if the patient does not have RIP. There may be an urgency, but the patient is in the lane and does not require resuscitation CPR. Normothermia can be used as well as a blood prime to maintain high oxygen delivery and normal iCa levels to maintain cardiac contractility.

ECPR patients are not in the lane and are often undergoing resuscitation CPR (that is, they have RIP). The extracorporeal strategy needed for dealing with RIP can be termed the three "C" strategy; cooling the patient, clear priming the pump to hemodilute the patient and using a calcium free perfusate. It can also be called the three "H" strategy; hypothermic hemodilution with hypocalcemia. The use of dantrolene should also be considered because it has significant protective effects against calcium stress.

Using a reperfusion strategy in an ECMO patient without RIP would unnecessarily expose that patient to hypothermia, hemodilution and hypocalcemia which could have iatrogenic sequelae.

ECPR REPERFUSION STRATEGY

COMBATING RIP WITH ECPR:
A TWO STEP PROCESS

1. STOP THE DYING (PREVENT REPERFUSION INJURY)

- Hypothermia
- Hemodilution
- Hypocalcemia
  - dantrolene

2. BRING BACK TO LIFE
(REVERSE THE RIP)

- Normalize venous pCO2
- Normalize venous pH
- Normalize hematocrit
- Normalize calcium
- Rewarm
- Continue support

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The three "H" strategy uses hypothermia, hemodilution and hypocalcemia to block the dying process; in other words, to prevent reperfusion injury from occurring during the subsequent resuscitation.   This is followed by the normalization of the venous pCO2 and venous pH which reactivates the antioxidants. The normalization of the hematocrit (increased oxygenation) can then be performed. The calcium is then normalized and, finally, normothermia is restored. Continued extracorporeal support in the form of ECMO will probably be needed since no strategy can completely negate all the injury from reperfusion.

HYPOTHERMIA PREVENTS REPERFUSION INJURY

- "Destructive processes following ischemia/reperfusion can be prevented or significantly mitigated by hypothermia"
  - Polderman, 2009
- Protective effects of mild to moderate hypothermia
  - ⬇ Mitochondrial injury & dysfunction
  - ⬇ Cerebral metabolism
  - ⬇ Influx of calcium
  - ⬇ Cell membrane leakage
  - ⬇ Cell edema
  - ⬇ Intracellular acidosis
  - ⬇ Production of ROS
- Many side effects of hypothermia (bradycardia, hypotension, reduced cardiac output, coagulopathy, non-uniform cooling) are non sequitur when the patient is supported by the pump

Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. Crit Care Med 2009;37:S186-202.

BACKGROUND: Mild to moderate hypothermia (32-35 degrees C) is the first treatment with proven efficacy for postischemic neurological injury. In recent years important insights have been gained into the mechanisms underlying hypothermia's protective effects; in addition, physiological and pathophysiological changes associated with cooling have become better understood.

OBJECTIVE: To discuss hypothermia's mechanisms of action, to review (patho)physiological changes associated with cooling, and to discuss potential side effects.

DESIGN: Review article.

INTERVENTIONS: None.

MAIN RESULTS: A myriad of destructive processes unfold in injured tissue following ischemia-reperfusion. These include excitotoxicty, neuroinflammation, apoptosis, free radical production, seizure activity, blood-brain barrier disruption, blood vessel leakage, cerebral thermopooling, and numerous others. The severity of this destructive cascade determines whether injured cells will survive or die. Hypothermia can inhibit or mitigate all of these mechanisms, while stimulating protective systems such as early gene activation. Hypothermia is also effective in mitigating intracranial hypertension and reducing brain edema. Side effects include immunosuppression with increased infection risk, cold diuresis and hypovolemia, electrolyte disorders, insulin resistance, impaired drug clearance, and mild coagulopathy. Targeted interventions are required to effectively manage these side effects. Hypothermia does not decrease myocardial contractility or induce hypotension if hypovolemia is corrected, and preliminary evidence suggests that it can be safely used in patients with cardiac shock. Cardiac output will decrease due to hypothermia-induced bradycardia, but given that metabolic rate also decreases the balance between supply and demand, is usually maintained or improved. In contrast to deep hypothermia (<or=30 degrees C), moderate hypothermia does not induce arrhythmias; indeed, the evidence suggests that arrhythmias can be prevented and/or more easily treated under hypothermic conditions.

CONCLUSIONS: Therapeutic hypothermia is a highly promising treatment, but the potential side effects need to be properly managed particularly if prolonged treatment periods are required. Understanding the underlying mechanisms, awareness of physiological changes associated with cooling, and prevention of potential side effects are all key factors for its effective clinical usage.

HYPOTHERMIA AND SAFE RESUSCITATION

Probability of Safe Resuscitation
(From the Australasian Society of Cardio-Vascular Perfusionists)
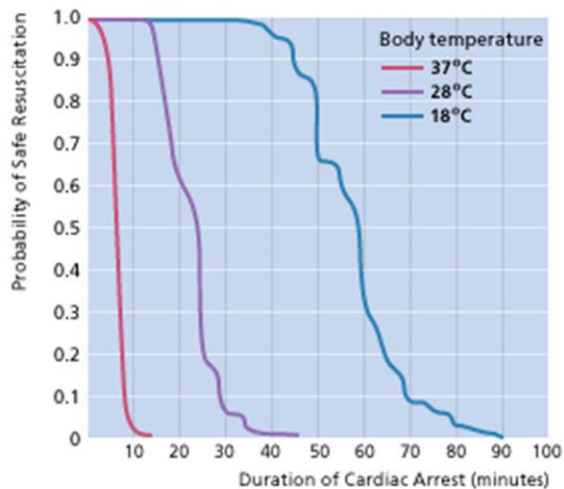
The probability of a safe arrest time is dependent upon the patient's temperature. At 37C, if CPR or extracorporeal support is not started within 5 minutes, there is a very high probably that resuscitation will not be successful or, if successful, not without significant brain damage. Cooling the patient can greatly increase the probability of safely restoring the patient.

THE RISK OF DELAYING HYPOTHERMIA
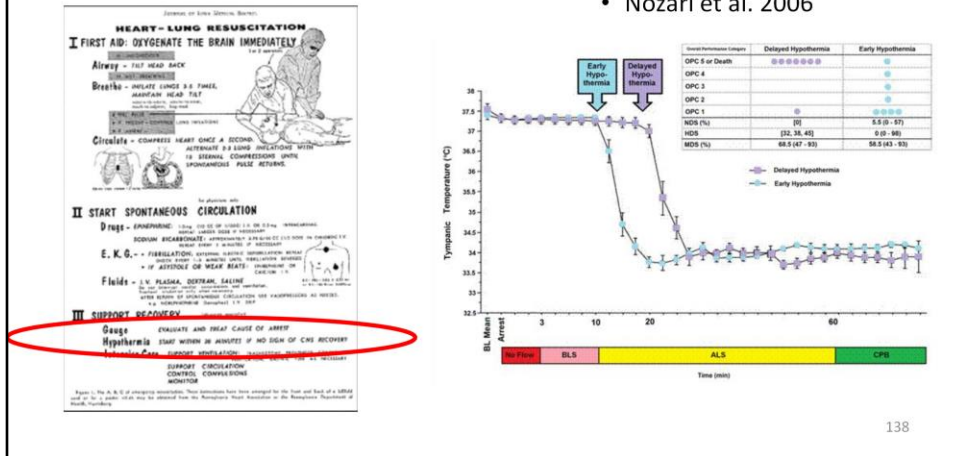
Dr. Peter Safar (1924-2003) together with James Elam developed resuscitation CPR as it is currently used throughout the world. It was first implemented at Johns Hopkins in 1959. A CPR poster dated to 1964 instructs that hypothermia be instituted if signs of CNS recovery are not evident within 20 minutes. Unfortunately the American Heart Association did not recommend implementing hypothermia until 2005, depriving patients the benefit of hypothermia for 40 years.

The importance of early hypothermia can be illustrated by a 2006 article by Nozari*. During experiments with dogs, hypothermia was induced by the intravenous administration of cold IV solution during CPR/BLS/ALS resuscitation. A delay of 10 minutes in administering the cold solution while doing CPR resulted in a much higher mortality rate compared to when hypothermia was induced 10 minutes earlier.

Most cardiac arrest patients will benefit from hypothermia induced during CPR by the administration 30 mls/Kg of ice cold crystalloid solution, whether the heart starts spontaneously or ECPR is instituted.

*Nozari A, Safar P, Stezoski SW, et al. Critical time window for intra-arrest cooling with cold saline flush in a dog model of cardiopulmonary resuscitation. Circulation. Jun 13 2006;113(23):2690-2696.

CPR COOLING VS. ECPR COOLING

- **CPR COOLING**

  - Blood flow ~ 40%

  - Cooling protects against 'too little' O2 delivery causing tissue anoxia

  - Depth of cooling limited to >32°C due to cardiac inhibition upon ROSC

- **ECPR COOLING**

  - Blood flow ~ 100%

  - Cooling protects against 'too much' O2 delivery causing reperfusion injury

  - Depth of cooling not limited by the need for cardiac recovery

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There is a difference between the need to cool a patient during conventional CPR and cooling when placed on ECPR. During resuscitation CPR the best blood flow to the brain that can be expected is about 40% of normal. However, once ECPR is started, blood flow approaching 100% of normal can be expected.

Cooling during CPR is performed to protect the organs from 'too little' O2 delivery by reducing the metabolic need for oxygen. Paradoxically ECPR cooling is needed to protect against 'too much' oxygen being delivered by the pump. Providing enough pump flow to maintain blood pressure will simultaneously deliver copious amounts of oxygen from the oxygenator compared to CPR even if a 21% FiO2 sweep gas is used. This will cause reperfusion injury in a patient with RIP. Hypothermia is the only proven clinical treatment to prevent reperfusion injury from this over oxygenation by the pump.

During CPR, cooling is limited to no less than 32-34°C. If the heart gets too cold, it may not adequately support a patient's hemodynamics upon ROSC. A recent trial of targeted hypothermia (33°C) used in pediatric brain trauma patients <u>without</u> cardiac arrest demonstrated significantly more hypotension and increased need for vasoactive agents than their normothermic counter-parts with almost twice as many deaths in the hypothermic group. This may have been related to poor cardiac function during hypothermia and the subsequent rewarming. However since cardiac function and ROSC are not primary concerns once ECPR is started, hypothermia need not be strictly limited.

ECPR HYPOTHERMIA

- Cool 'perfusate' rapidly removes CO_2 from tissues
  - CO_2 is more soluble at temperatures below 37°C

- Metabolic rate reduced by hypothermia
  - CO_2 production reduced
  - O_2 need reduced
  - Neutrophil inflammatory response reduced
  - Apoptosis slowed

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Hypothermia is used during resuscitation CPR to compensate for low oxygen delivery. However once a patient is on ECPR, oxygen delivery is no longer a problem. So why the need for hypothermia? Hypothermia is the only proven method of protection against reperfusion injury. So once ECPR is implemented, hypothermia is used to protect against too much oxygen delivery. Core cooling is the most efficient means of inducing global hypothermia. And the quickest way to implement core cooling is the use of a pump with cool perfusate. Infants and small children can be quickly cooled by starting support with the pump primed with room temperature perfusate. However larger patients may require active cooling through the oxygenator to overcome the heat sink of their bodies.

During ECPR, perfusate cooler than the body rapidly removes CO_2 from the tissues because CO_2 is more soluble in cooler fluids. As the cool perfusate circulates thru the patient's body it picks up CO_2 which then passes into the oxygenator where it is removed by a high sweep gas flow with a low (room air) FiO_2. Additional benefits of hypothermia include slowing apoptosis and the reducing the inflammatory response.

How cold is cold enough? The American Heart Association suggests topical cooling to 32-34°C during conventional CPR. Any colder and cardiac function (should it recover) may be compromised. However with ECPR the recovery of cardiac function is not an immediate concern. Therefore cooler temperatures can be employed, if desired. The degree of hypothermia that is necessary probably depends on the level of RIP present. However that number has yet to be determined. Theoretically the farther a patient lies outside the lane, the cooler the temperature needs to be to prevent reperfusion injury.
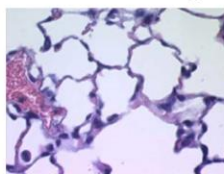
ECPR HEMODILUTION: CLEAR PRIME
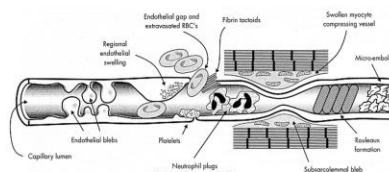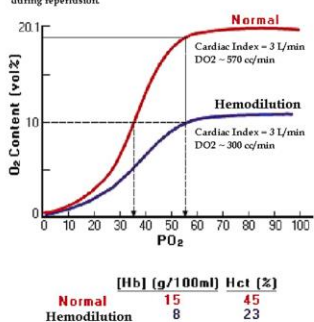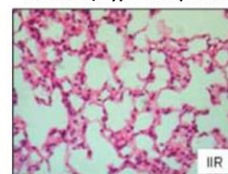
Hemodilution reduces the amount of oxygen that the blood can carry. This allows for a high pump blood flow rate without excessive oxygen delivery to the tissues where it can generate ROS in the RIP patient. High pump blood flow is needed to ensure quick core cooling and efficient CO2 removal from the tissues. However until these two protective strategies are fully implemented, the delivery of oxygen needs to be minimized. The chicken cardiac myocyte experiment demonstrated that continued anoxia is less lethal to ischemic cells than the sudden reintroduction of even moderate amounts of oxygen. Hemodilution is a method to prevent the reintroduction of excessive oxygen while allowing efficient cooling and CO2 removal.

Hemodilution also combats no reflow phenomenon. Blood with a low hematocrit is better able to navigate the obstacles present in damaged capillaries. Resuscitation CPR patients placed on extracorporeal support often manifest a pulmonary hemorrhage after a short period of time, from a few minutes to a few hours. This is probably due to a no reflow phenomenon in the lungs when blood is being pumped thru damaged capillaries that eventually rupture under the stress of perfusion. The same phenomenon can occur in the brain resulting in intracranial hemorrhage. Hemodilution may help to prevent this by reducing the high resistance to flow caused by thick blood traversing the damaged capillaries.

ECPR HYPOCALCEMIA:
CALCIUM FREE PRIME & DANTROLENE

- Calcium free prime reduces intracellular migration to combat cardiac & CNS damage.
- Calcium stress is more lethal than oxygen stress.

Neuronal Cell Culture: Survival After 12 Hours Oxygen-Glucose Deprivation

Wang et al. 2002
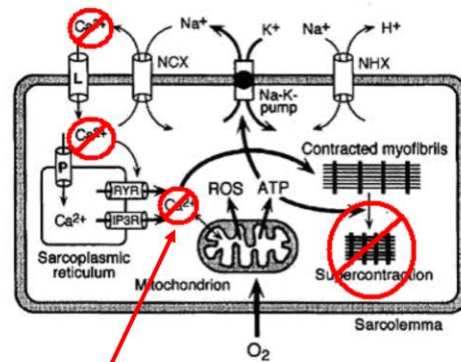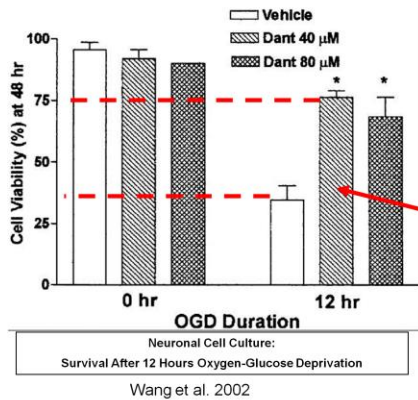
Dantrolene blocks ryanodine receptor sites which prevents intracellular Ca+2 fluxes and stops the formation of the MPTP.

Dantrolene reduces neuronal cell death from hypoxic/ischemia.

Muehlschlegel & Sims. 2009

Calcium is the unrecognized villain in reperfusion injury and is probably the most difficult to control. The use of a calcium free perfusate in the pump is one intervention that ECPR can utilize in an attempt to reverse the calcium flux into the ischemic cells.

The calcium is released into cells through ryanodine receptors (RyRs) which are calcium channels present in excitable tissues like cardiac myocytes, cardiac conduction cells and central nervous system neurons. RyRs are the major cellular mediators of calcium-induced calcium release in animal cells. During reperfusion there is an uncontrolled increase in cytosolic calcium known as a "calcium spark". The calcium spark causes mitochondrial permeability transition pores (MPTP) to open uncontrollably. The leaking mitochondrial membranes cause swelling, ATP release and accelerated cell death (apoptosis).

A drug that holds promise for dealing with calcium stress is Dantrolene sodium. Dantrolene is a drug that specifically blocks the flow of calcium through the RyR channels and prevents the MPTP from opening. Normally used to block the hypermetabolic effects of variants of malignant hyperthermia, Dantrolene has been shown to have protective effects on ischemic cardiac and neural cells. Dantrolene has few side effects and may have the potential to become useful in the prevention of reperfusion injury of all kinds, from transplant organs to patients undergoing CPR.

In an experiment by Wang et al in 2002, a control culture of neurons and 2 experimental Dantrolene treated neuronal cultures were subjected to 12 hours of simulated hypoxic/ischemia. Forty-eight hours after reintroducing oxygen the surviving cells were counted. Only about 30% of the control culture cells were viable, but 75% of the Dantrolene treated cells were still alive. Assuming that the Dantrolene successfully blocked the effects of calcium stress, the non-viable cells in the experimental cultures probably succumbed to oxygen stress which Dantrolene cannot suppress. This experiment suggests that Dantrolene can significantly ameliorate reperfusion injury damage and that calcium stress is about twice as deadly as oxygen stress in causing cell death from reperfusion injury.

MH Resuscitation Strategy		ECPR Reperfusion Strategy	
A. Multiple intravenous, ice cold, normal saline fluid boluses.	1. Dilutes elevated blood K+ which is the primary cause of cardiac arrest. (NS is K and Ca free). 2. Dilutes myoglobin from muscle breakdown which can cause clogging of vital capillaries. 3. Induces mild hypothermia to counter-act hyperthermia and reduce the hypermetabolic oxygen consumption and CO2 production.	A. Calcium free crystalloid pump prime at room temperature.	1. Dilutes Ca+2 to reduce intracellular Ca+2 influx; a cause of calcium stress and dilutes RBCs to reduce over oxygenation; a cause of oxygen stress. 2. Dilutes formed elements in the blood to combat no reflow phenomenon (DIC) which can block vital capillaries. 3. Induces mild hypothermia to combat reperfusion injury and reduce oxygen consumption.
B. Enhanced ventilation.	1. Reduces build up of CO2 to correct acidosis caused by hypermetabolism.	B. High pump blood flow and high sweep gas flow.	1. Reduces tissue CO2 build up which is the primary cause of intracellular acidosis.
C. Since 1982, intravenous dantrolene; 90% mortality to 90% survival.	1. Blocks the ryanodine receptor to prevent the release of calcium associated with hypermetabolism in skeletal muscle. 2. Does not interfere with cardiac function and may enhance the ROSC. 3. Few side effects. 4. Safe to give prophylactically.	C. Since 12/2011, dantrolene in the ECPR pump prime. ECPR or Extremis ECMO survival: No dantrolene: 7/33 = 21% or 12/33 = 36% w/ late death (30days). Prime dantrolene: 4/6 = 67%	1. Blocks the ryanodine receptor to prevent the release of calcium associated with calcium stress related reperfusion injury in the brain and other vital organ systems. 2. Does not interfere with cardiac function and may enhance the ROSC. 3. Few side effects. 4. Safe to give prophylactically.

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   The drug Dantrolene sodium holds the most promise for dealing with calcium stress. It is added to the prime in the ECPR pump. Dantrolene is an FDA approved drug best known as a treatment for malignant hyperthermia (MH) and its variants. After the widespread introduction of Dantrolene, the mortality from malignant hyperthermia fell from 90% to less than 10%. MH patients commonly receive repeated doses of Dantrolene during their resuscitation. In addition, patients experiencing MH commonly receive infusions of ice cold normal saline to prevent any temperature elevation and to keep their blood potassium low. In spite of this, some MH patients experience cardiac arrest due to the greatly elevated blood potassium levels caused by muscle breakdown from MH and require CPR. Unlike other types of cardiac arrest patients whose survival is doubtful after 30 minutes of CPR, extended CPR for up to two hours in MH patients frequently has successful outcomes. This is probably because the MH resuscitation strategy using hypothermia, hemodilution and Dantrolene protects the MH patient from reperfusion injury. This same type of resuscitation strategy would benefit non-MH patients needing CPR resuscitation and/or ECPR.

CASE REPORT #1

11 Y/O UNDERGOING ABLATION IN CATH LAB. LMCA OCCLUSION.

DATE	TIME	TOTAL TIME MIN.	TEMP	BLOOD GAS	pH	pCO2	pO2	Base	HCT	iCa	COMMENT
1st day	~ 10:30	0	37						35		PT. CODES IN CATH LAB. TRANSPORTED TO OR DURING CPR FOR EMERGENT ECPR/CPB.
	11:10	40	37	ABG	7.01	72	43	-15.1			Corrected Anion Gap = 16 mEq/L
	11:51	81	37	VBG	6.90	113	18	-11	22	1.11	ON ECPR/CPB, LIMA >LCA REPAIR
	11:59	89	33	VBG	6.98	63	23	-15.9	25	0.98	
	12:09	99	30	VBG	7.13	44	36	-13.8	26	1.04	
	12:20	110	24	VBG	7.22	35	48	-12.4	25	1.02	
	12:39	129	26	VBG	7.33	31	64	-8.9	24	1.00	
	13:02	152	26	VBG	7.32	28	67	-11.5	29	0.98	
	13:29	179	26	VBG	7.39	26	61	-9.8	31	0.79	
	13:42	192	25	VBG	7.42	23	113	-9.4	31	0.88	
	13:54	204	25	VBG	7.49	23	115	-6.3	31	0.88	
	14:12	222	31	VBG	7.4	27	46	-8.1	29	1.59	
	14:23	233	37	VBG	7.38	36	39	-4	32	1.32	
	14:38	248	37	VBG	7.37	36	36	-4.1	32	1.29	
	15:24	294	37								OFF ECPR/CPB, ON ECMO
	22:00		HIGHEST LACTIC ACID = 13 mmol/L								
2nd day			SEDATION STOPPED. PT. AWAKES NERUOLOGICALLY INTACT.								
3rd day			TRANSPORTED ON ECMO TO ARKANSAS/TEXAS FOR HEART & KIDNEY TX. SURVIVES NEURLOGICALLY INTACT.								

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This is an illustration of how hypothermia, hemodilultion and hypocalcemia can be used to combat RIP. In this case report an 11 year old patient undergoing ablation in the cardiac catheterization laboratory experienced a sudden left main coronary artery (LMCA) occlusion necessitating the institution of resuscitation CPR. After 81 minutes of CPR the patient was placed on ECPR/CPB and immediately cooled to 24°C while repairs were made to the LMCA. Venous blood gases drawn during this time period demonstrated the large amount of CO2 built up in the tissues during CPR, confirming the presence of RIP. This excess CO2 was removed as the patient was cooled, normalizing the venous pH and pvCO2 and reactivating intracellular antioxidants. Hemodilution was used to combat no reflow phenomenon, dropping the hematocrit from 35% to 22% after going on pump. The ionized calcium was kept low to reduce calcium stress.

While the patient was cool and after the venous pH and pvCO2 were normalized, the hematocrit was increased. Lastly during rewarming the ionized calcium was normalized. Cardiac function failed to return. Therefore the patient was transferred to a regular closed system ECMO pump for continued support. No pulmonary hemorrhage (a telltale sign of pulmonary reperfusion injury) developed. During the second day of ECMO support, the heart and kidneys were deemed irreversibly damaged. Sedation was stopped and the patient was allowed to awaken and found to be neurologically intact. The patient was subsequently transported on ECMO to a transplant center on the third day of extracorporeal support where she eventually received a successful heart and kidney transplant.

CASE REPORT #2

6 HRS S/P NW1, EMERGENT ECPR, WT = 2.6 KG

TIME	COUNT DOWN	TEMP		pH	pCO2	pO2	BASE	CO2 GRAD	HCT	iCa	ANION GAP	LACTIC ACID	COMMENT
1432	-380	37											OFF CPB
1442	-370	37	ABG	7.38	45	<33	0.7	7	35	1.42	14		LAST BLOOD GASES IN OR
			VBG	7.35	52	<33	2						
1650	-242	37	ABG	7.35	48	<33	-0.2	13	50	1.41	13	3.7	~1 HR POSTOP
			VBG	7.29	61	<33	0.4						
1750	-182	37	ABG	7.36	37	<33	-4.2	19					~2 HR POSTOP
			VBG	7.27	56	<33	-2.2						
1940	-72	37	ABG	7.31	21	38	-14.7	53					~4 HR POSTOP
			VBG	7.01	74	<33	-14.4						
2016	-36	37											MINI CODE
2052	0	37											CODE CALLED, CPR STARTED
2125	33	28	VBG	7.05	46	71	-17						STARTED ON ECPR PUMP, COOLING
2141	49	30	VBG	7.14	55	61	-9.7						ON ECPR PUMP
2214	82	32	VBG	7.2	36	43	-13.4						ON ECPR PUMP
2230	100	32	ABG	7.2	30	84	-14.8	0	16			21.1	ON ECPR PUMP
			VBG	7.24	30	54	-14.7						
2334													TRANSFER TO ECMO PUMP
0005	195	32	ABG	7.22	35	98	-14.9	1	39	1.04			ON ECMO PUMP
			VBG	7.23	36	44	-15.6						ON ECMO PUMP
1030	625	32	ABG	7.38	36	221	-3.6	4		1.44	19	14.2	ON ECMO PUMP
			VBG	7.39	40	40	-0.8						ON ECMO PUMP

SUCCESSFULLY WEANED FROM ECMO AFTER 135 HOURS

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In this case report a 2.6 kg infant underwent a Norwood stage one procedure for hypoplastic left heart syndrome. The time till cardiac arrest is represented as a "count down". The last set of blood gases (ABG and VBG drawn at the same time) in the operating room document normal values with the exception of low pO2 values. These are normal pO2 values for this type of mixing lesion. The p[v-a]CO2, the hct, the iCa and the anion gap are all normal at T minus 370 minutes till arrest. At T minus 242 minutes, the p[v-a]CO2 increased to 13 mmHg and the lactic acid was slightly elevated at 3.7 mmol/L. The patient received a blood transfusion to increase the hct to 50%. At T minus 182 minus, the p[v-a]CO2 increased to 19 mmHg and a base deficit was beginning to develop. In retrospect, the frequency of lab analysis should have been increased at this time to at least every 60 minutes and serious consideration should have been given to starting VA ECMO. At T minus 72 minutes, the p[v-a]CO2 was 53 mmHg and the base deficit increased to -14 mEq/L, prompting a call to the surgeon suggesting the implementation of ECMO. Before ECMO could be started, the patient arrested 380 minutes after coming off CPB. After 33 minutes of CPR the patient was placed on ECPR and cooled to 28C and the hct dropped to 16%. Over the next 100 minutes of ECPR the patient's temperature was stabilized at 32C and the venous pH and pvCO2 were normalized. The patient was transferred to a regular ECMO pump and the hct normalized. The patient's iCa was normalized 625 minutes after arresting. The patient spent an additional 125 hours on ECMO, followed by successful weaning and discharge from the hospital without detectable cardiac or CNS morbidity.
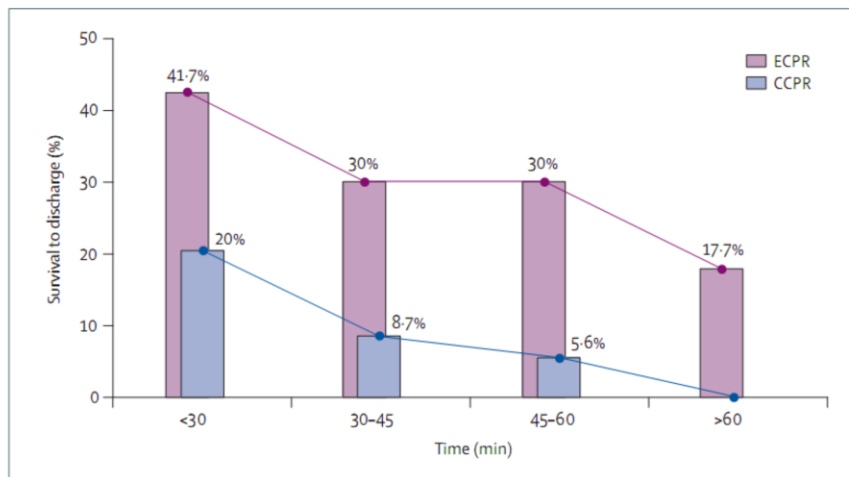
ECPR and Survival
Chen et al. 2008

Figure 1: Relation between CPR duration and the survival rate to discharge
ECPR=extracorporeal CPR. CCPR=conventional CPR.

A meta-analysis by Chen et al in 2008 compared the survival of patients placed on ECPR to treatment with in-hospital resuscitation CPR/ACLS. Probably none of the ECPR patients received a formalized reperfusion strategy of hypothermia, hemodilution and hypocalcemia. However the results were still superior to CPR. If a uniform reperfusion strategy can be widely adopted, the potential for in-hospital survival could be greatly improved.
Even cardiac arrest CPR patients presenting out-of-hospital can be cooled and hemodiluted during transport to the emergency room where a surgeon and perfusionist could be waiting to implement a successful reperfusion strategy using ECPR if conventional resuscitation efforts fail.

EPILOG & WARNING
Baron Victor Von Frankenstein*

– His vision: "Life and death appeared to me ideal bounds, which I should first break through, and pour a torrent of light into our dark world."

– His reality: "I saw the hideous phantasm of a man stretched out, and then, on the working of some powerful engine, show signs of life, and stir with a uneasy, half vital motion."

- *Frankenstein, or The Modern Prometheus,* March, 1818
  – Mary Wollstonecraft Shelley

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Lastly, here is a warning for those attempting to expand the envelope of survival by deliberately placing patients who are essentially dead (based on the AHA and PALS guidelines) on extracorporeal support. We need to be reminded of a story we are all familiar with. The Baron's vision was to help mankind and bring light "into our dark world". Instead his "powerful engine" created a brain damaged monster.

As we use our powerful engines (ECPR pumps) to retrieve patients from the brink of death, we do not want to create any brain damaged monsters. That is why it is vital that we understand the nature of reperfusion injury and address it with an effective strategy that leaves patients intact, both in mind and in body.

REFERENCES

1. Becker LB, New concepts in reactive oxygen species and cardiovascular reperfusion physiology. Cardiovascular Research 61 (2004);461 470
2. http://www.benbest.com/cryonics/ischemia.html#reperfuse
3. http://www.thoracic.org/sections/clinical-information/critical-care/critical-care-research/animal-models-of-acute-lung-injury.html
4. Mura et al. Critical Care 2006 10:R130
5. Lamia B, Minerva Anestesiol 2006
6. Schneider D. Limits of resuscitation. I. Thanatophysiologic and therapeutic limits. Z Gesamte Inn Med. 1981 May 15;36(10):305-10.
7. AHA Circulation, 2005. 112(24 Suppl): p. IV1-203.
8. AHA Pediatrics, 2006. 117(5): p. e989-1004.
9. Idris AH et al. Crit Care Med 2005; 33(9):2043-8.
10. Becker, L.B.,Cardiovasc Res, 2004. 61(3): p. 461-70.
11. KH Polderman, Crit Care Med 2009 37:7(Suppl), S188
12. Nozari A, Safar P, Stezoski SW, et al. Critical time window for intra-arrest cooling with cold saline flush in a dog model of cardiopulmonary resuscitation. Circulation. Jun 13 2006;113(23):2690-2696.
13. Wang et al. Journal of Cerebral Blood Flow & Metabolism (2002) 22, 206–214; doi:10.1097/00004647-200202000-00008
14. Muehlschlegel S, Sims JR. Dantrolene: mechanisms of neuroprotection and possible clinical applications in the neurointensive care unit. Neurocrit Care 2009;10:103-15.
15. Morris MC, Wernovsky G, Nadkarni VM. Survival outcomes after extracorporeal cardiopulmonary resuscitation instituted during active chest compressions following refractory in-hospital pediatric cardiac arrest. Pediatr Crit Care Med 2004;5:440-6.
16. Chen YS, Lin JW, Yu HY, et al. Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis. Lancet 2008;372:554-61.
17. Cabanas JG, Brice JH, De Maio VJ, Myers B, Hinchey PR. Field-induced Therapeutic Hypothermia for Neuroprotection after Out-of Hospital Cardiac Arrest: A Systematic Review of the Literature. J Emerg Med.
18. Grist G, Whittaker C, Merrigan K, Fenton J, Pallotto E, Lofland G. Defining the late implementation of extracorporeal membrane oxygenation (ECMO) by identifying increased mortality risk using specific physiologic cut-points in neonatal and pediatric respiratory patients. J Extra Corpor Technol 2009;41:213-9
19. Grist G, Whittaker C, Merrigan K, et al. Identifying neonatal and pediatric cardiac and congenital diaphragmatic hernia extracorporeal membrane oxygenation patients at increased mortality risk. J Extra Corpor Technol;42:183-90.
20. Halestrap AP. Calcium, mitochondria and reperfusion injury: a pore way to die. Biochem Soc Trans 2006;34:232-7.

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1. Becker LB, New concepts in reactive oxygen species and cardiovascular reperfusion physiology. Cardiovascular Research 61 (2004);461 470
2. http://www.benbest.com/cryonics/ischemia.html#reperfuse
3. http://www.thoracic.org/sections/clinical-information/critical-care/critical-care-research/animal-models-of-acute-lung-injury.html
4. Mura et al. Critical Care 2006 10:R130
5. Lamia B, Minerva Anestesiol 2006
6. Schneider D. Limits of resuscitation. I. Thanatophysiologic and therapeutic limits. Z Gesamte Inn Med. 1981 May 15;36(10):305-10.
7. AHA Circulation, 2005. 112(24 Suppl): p. IV1-203.
8. AHA Pediatrics, 2006. 117(5): p. e989-1004.
9. Idris AH et al. Crit Care Med 2005; 33(9):2043-8.
10. Becker, L.B.,Cardiovasc Res, 2004. 61(3): p. 461-70.
11. KH Polderman, Crit Care Med 2009 37:7(Suppl), S188
12. Nozari A, Safar P, Stezoski SW, et al. Critical time window for intra-arrest cooling with cold saline flush in a dog model of cardiopulmonary resuscitation. Circulation. Jun 13 2006;113(23):2690-2696.
13. Wang et al. Journal of Cerebral Blood Flow & Metabolism (2002) 22, 206–214; doi:10.1097/00004647-200202000-00008
14. Muehlschlegel S, Sims JR. Dantrolene: mechanisms of neuroprotection and possible clinical applications in the neurointensive care unit. Neurocrit Care 2009;10:103-15.
15. Morris MC, Wernovsky G, Nadkarni VM. Survival outcomes after extracorporeal cardiopulmonary resuscitation instituted during active chest compressions following refractory in-hospital pediatric cardiac arrest. Pediatr Crit Care Med 2004;5:440-6.
16. Chen YS, Lin JW, Yu HY, et al. Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis. Lancet 2008;372:554-61.
17. Cabanas JG, Brice JH, De Maio VJ, Myers B, Hinchey PR. Field-induced Therapeutic Hypothermia for Neuroprotection after Out-of Hospital Cardiac Arrest: A Systematic Review of the Literature. J Emerg Med.
18. Grist G, Whittaker C, Merrigan K, Fenton J, Pallotto E, Lofland G. Defining the late implementation of extracorporeal membrane oxygenation (ECMO) by identifying increased mortality risk using specific physiologic cut-points in neonatal and pediatric respiratory patients. J Extra Corpor Technol 2009;41:213-9
19. Grist G, Whittaker C, Merrigan K, et al. Identifying neonatal and pediatric cardiac and congenital diaphragmatic hernia extracorporeal membrane oxygenation patients at increased mortality risk. J Extra Corpor Technol;42:183-90.
20. Halestrap AP. Calcium, mitochondria and reperfusion injury: a pore way to die. Biochem Soc Trans 2006;34:232-7.