
Pre-Oxygenated Crystalloid Cardioplegia

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Abstract

Since 1982, oxygenated crystalloid cardioplegia solution has become a popular method of myocardial preservation during cardiac surgery. The preferred method of oxygenated cardioplegia delivery has been the use of a recirculating delivery circuit that bubbles or films oxygen into the solution. Our present method allows us to pre-oxygenate the cardioplegia solution bags up to two weeks before using the oxygenated solution. The pO₂ remains between 650-850 mmHg, and the oxygen content remains at 3.0-4.0 vol.%. The oxygenated cardioplegia maintains its sterility for as long as two weeks. The cost of oxygenating the cardioplegia is less than \$1 per bag. Our delivery circuit requires no recirculating pump or sophisticated circuitry.

Introduction

The use of oxygenated crystalloid cardioplegia solution (OCPS) has increased over the past six years (1-8). The benefits of OCPS over blood cardioplegia include: 100% availability of the delivered oxygen for metabolism; improved flow distribution because of lower viscosity; simpler delivery system; and the ability to filter particulate matter, bacteria, and bacterial endotoxins, using a 0.2 micron cardioplegia filter.

The addition of oxygen to crystalloid cardioplegia has required the use of a hardshell cardioplegia reservoir that allows oxygen to be either blown into the air space (film oxygenation) or bubbled into the solution (bubble oxygenation), as the solution recirculates around the delivery system (3,7). The hospital cost of these disposable delivery systems can run between \$75 and \$200.

The non-recirculating cardioplegia delivery system we have used for the past eight years includes a pressurized cardioplegia solution bag attached to a spiked drip chamber with administration line ending at the cardioplegia needle (a).

A perfusion adapter line is attached to a stopcock sideport situated proximal to the cardioplegia needle. The adapter line, when circuited through a roller pump, acts as an aortic root vent

pathway during the x-clamp period (Figure 1).

Our goal was to update our cardioplegia solution (CPS) by incorporating a static oxygenation technique and a 0.2 μ cardioplegia filter (b), and modifying the solute content (altered to optimize myocardial protection and oxygen delivery) without changing our delivery method (Table 1).

Method

During this exercise, we conducted a series of trials to determine the best technique for oxygenating the CPS:

1. The most appropriate oxygen gas mixture for static CPS oxygenation.
2. The optimal mixing time required to reach maximum oxygen saturation of the CPS.
3. The optimal temperature to mix the oxygen with the CPS to achieve the desired pO₂ and O₂ content.
4. The effect of prolonged 4°C refrigeration on pO₂ levels with all the excess gas removed from the OCPS .
5. Whether visible gas comes out of solution oxygenated at different temperatures, when these solutions are cooled to 4°C and run through a non-recirculating CPS administration circuit, and allowed to warm to room temperature.
6. The effects on pO₂ levels over a two week period when various sizes of oxygen gas bubbles remain in the 4°C refrigerated OCPS bags.

In Trial #1, the hospital pharmacy prepared eight 500 ml. cardioplegia bags to our specifications. When the additives, and Baxter Healthcare's standard overfill (45 ml.) were taken into account, the actual fluid volume in our test CPS bags was approximately 600 ml. Four bags were cooled to 4°C and four kept at room temperature (20-24°C). Initially, we used two different mixtures of oxygen. One was 100% oxygen and the other was a 95% O₂ and 5% CO₂ mixture. Two bags from each specific temperature group were mixed with 100% oxygen and the other two bags from each temperature group were mixed with the 95% O₂ and 5% CO₂ mixture. Before we added the gas mixtures to the cardioplegia solutions, a CPS gas sample was

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drawn and the results tabulated. We added the gas mixtures, took CPS gas samples, and compared the results.

We added the gas mixtures (100% O₂ or 95% O₂, 5% CO₂) in the following fashion. From the gas mixture source, 1/4" tubing carried the gas mix to a hydrophobic bacterial filter (c). The filter was attached to a 21 gauge needle. We placed the needle into the cardioplegia bag injection port. The gas was bubbled into the 500 ml. CPS bag at a rate of less than one liter per minute. We pulled the needle from the port when the CPS bag became firm and distended. We picked each bag up and agitated the bag vigorously for 30 seconds to two minutes to determine an effective time period to completely saturate the CPS.

Once we mixed each bag for its prescribed time, we removed the undissolved gas from the CPS bags with a 21 gauge needle attached to a 3 cc. syringe barrel. A gas sample was drawn from each bag and the results compared and tabulated.

In Trial #2, once we selected the desired gas mixture (100% O₂), the pharmacy prepared another group of six CPS bags. We oxygenated three CPS bags at room temperature with a 60 ml. gas bubble left in the bag, and gas samples were drawn. We oxygenated the other three CPS bags at room temperature, all the excess gas was removed and samples were drawn. These six CPS bags were placed in a 4°C refrigerator. We removed each CPS bag from the refrigerator, agitated the bag for 30 seconds, and gas samples were taken at daily intervals for up six days.

In Trial #3, the pharmacy prepared six more CPS bags. We oxygenated three bags at 4°C and three bags at room temperature, then chilled them to 4°C. All six bags were run through our standard cardioplegia filter/administration set. The administration line was clamped when each bag emptied by 50%. The solution sat in the line for 20-30 minutes to see if visible gas would come out of solution as it warmed to room temperature.

In Trial #4, six additional CPS bags were injected and mixed with the gas at room temperature with various amounts of undissolved gas remaining in the CPS bags. The OCPS bags were cooled to 4°C. We removed the OCPS bags from the refrigerator, agitated them vigorously for 30 seconds, and took OCPS gas samples daily to compare the effect of gas bubble size on pO₂ levels over a two week period of time.

During the four trials, the various combinations of refrigerated OCPS were inspected daily for a two week period for sedimentation and discoloration, and standard cultures were run to determine the sterility of the oxygenated CPS at the end of two weeks. We also checked the bags at the end of two weeks for component degradation.

Oxygen Content

We calculated the oxygen content of the crystalloid cardioplegia solution differently than the oxygen content of blood cardioplegia. First, oxygen content of blood is determined by two carriers: oxyhemoglobin and the blood plasma, where crystalloid cardioplegia has only dissolved

oxygen. Second, the molar concentration of the cardioplegia solution, be it crystalloid or blood, will affect the dissolved oxygen content of the solution. As the molar concentration of a specific solution increases, the solubility coefficient of dissolved oxygen decreases, resulting in a lower calculated oxygen content for higher molar concentration solutions (9).

We used the following formula to determine the oxygen content of our OCPS at various pO₂'s (7):

O₂ Content (vol.%) =

$$\frac{[pO_2(\text{mmHg}) \times \text{Solubility Coefficient}(\lambda) * 1 \times 100]}{\text{Barometric Pressure}(760\text{mmHg}) - \text{Water Vapor Pressure}}$$

*Where (λ) is the solubility coefficient of oxygen in a particular molar concentration at a specified temperature.

In our case, the solubility coefficient of oxygen of our OCPS with a 370 mOsm. (0.370 N) molar concentration at 4°C was 0.0357 (Figure 2)*. The (λ) solubility coefficient is better known as the Ostwald solubility coefficient (10) which equals the mls. of gas dissolved in one ml. of solution under the temperature and pressure conditions which the dissolution takes place. Since the effect of water vapor pressure in our OCPS solution was negligible at 4°C, it was not a consideration in our oxygen content calculations.

Results

Following Trial #1, when we compared the gas results between the two oxygen mixtures (100% O₂ and 95% O₂/5% CO₂), we noted a significant difference in pH, pCO₂, pO₂ and base excess (Table II). The 95% O₂/5% CO₂ gas mixture decreased the pH and increased the pCO₂, creating a more acidic solution than desired. The 100% O₂ gas had the opposite effect. The pH increased while the pCO₂ decreased, creating a more alkaline solution.

As seen in Table II, the oxygen levels in the CPS test solutions that were cooled to 4°C before oxygenation increased significantly. The pO₂ was >1000 mmHg. and the O₂ content calculated to a range of 5.8-6.2 vol.%. The O₂ content was a significant improvement over the O₂ content of the non-oxygenated CPS (1.0 vol.%). When we oxygenated a bag of room temperature CPS, the pO₂ measured between 786-850 mmHg., while the O₂ content was 3.69-4.00 vol.%.

While testing the 30 second to two minute gas/solution mixing time range, we found 30 seconds to be the optimal time period. Any mixing time longer than 30 seconds did not significantly improve the pO₂ or O₂ content.

During Trial #2, the CPS bags oxygenated at room temperature with all the undissolved gas removed showed a significant drop in O₂ content and pO₂ during the six day period (Figure 3). In most cases, the pO₂ dropped below 650 mmHg. and the O₂ content below 3.0 vol.%, which we

* The curves for the following graph are drawn from the data in *Respiration*. The curve for CPS #1 was extrapolated from the tables in *Respiration and Circulation*, FASEB, 1971.

Figure 1

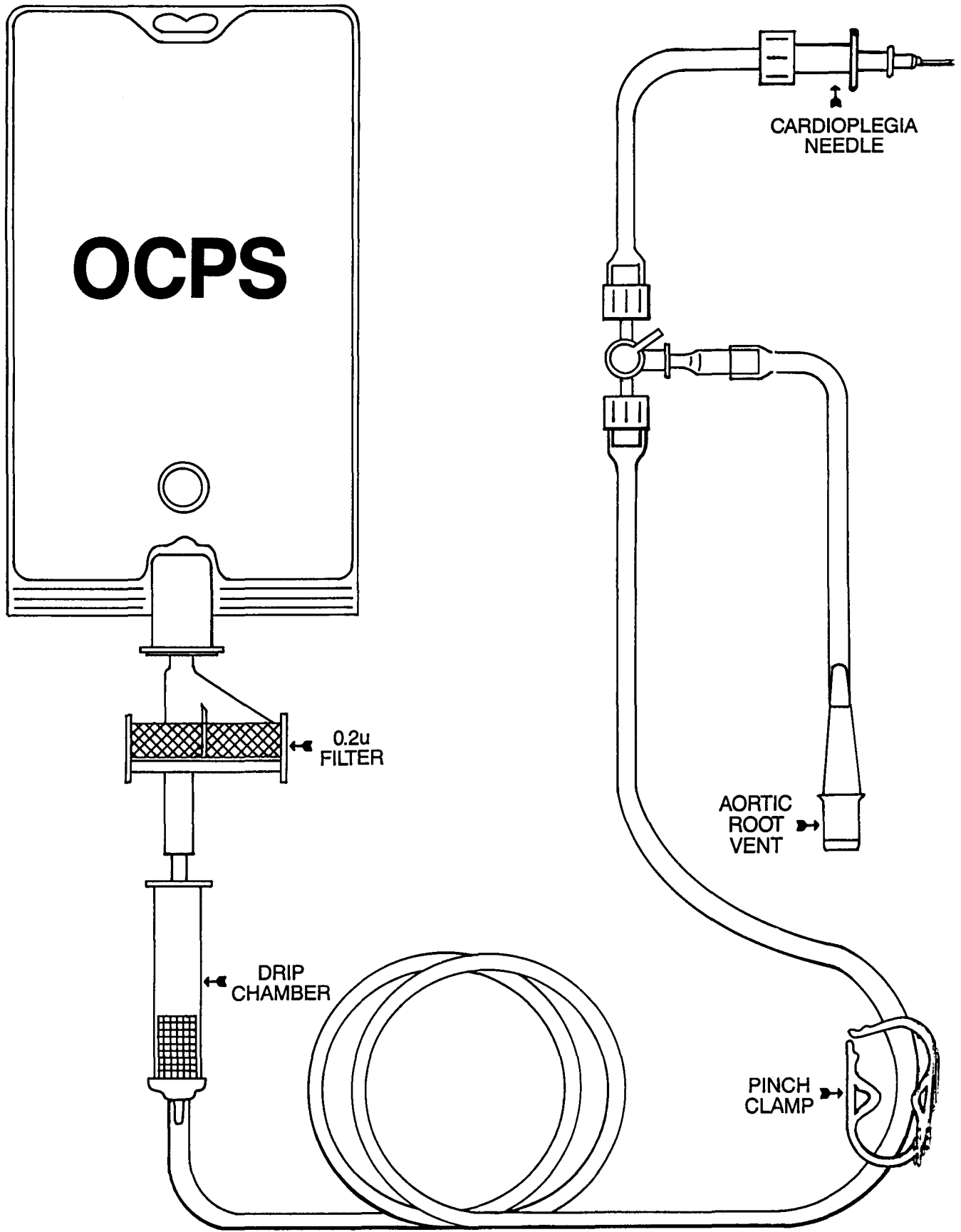


Figure 2

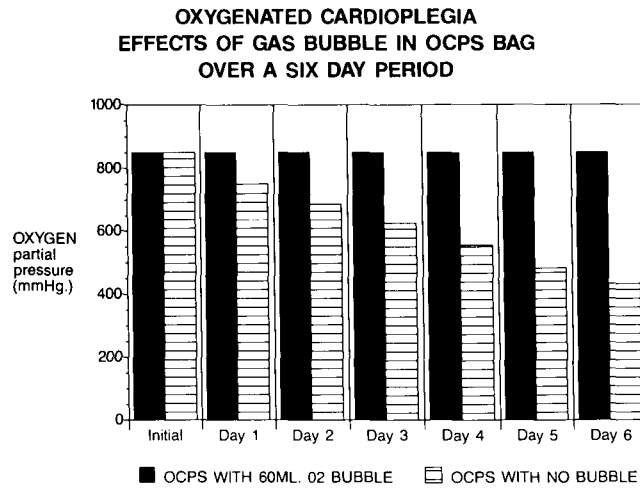


Figure 3

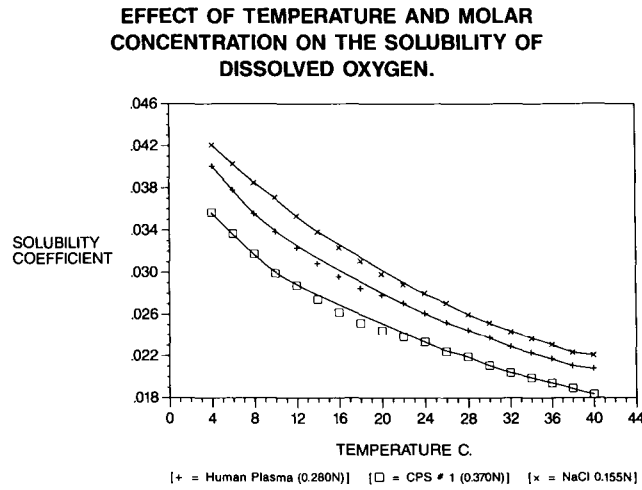


Table 1

TABLE 1
CARDIOPLEGIA SOLUTIONS

SOLUTE	PRIOR CPS	OCPS # 1	OCPS # 2
SODIUM	163 mEq./L.	115 mEq./L.	116 mEq./L.
CHLORIDE	152 mEq./L.	105 mEq./L.	95 mEq./L.
POTASSIUM	18 mEq./L.	20 mEq./L.	10 mEq./L.
BICARBONATE	22 mm /L.	27 mEq./L.	27 mEq./L.
MAGNESIUM	0	8 mEq./L.	4 mEq./L.
CALCIUM	0	0.25 mEq./L.	0.25 mEq./L.
MANNITOL	0	12.5 Gr./L.	12.5 Gr./L.
GLUCOSE	17 Gr./L.	5.0 Gr./L.	5.0 Gr./L.
LIDOCAINE	500 mg./L.	400.0 mg./L.	300.0 mg./L.
OXYGEN	1.0 vol.%	4.0 vol.%	4.0 vol.%
OSMOLALITY	400 mOsm./L.	370.0 mOsm/L.	340.0 mOsm/L.

1. Prior CPS is the non-oxygenated CPS used prior to this study.
2. OCPS # 1 is the initial cardioplegia given to stop the heart
3. OCPS # 2 is the maintenance CPS given in the follow-up doses.
4. The base solution for OCPS #1 & #2 is 0.45% NaCl. from Baxter Healthcare.

considered undesirable. The CPS bags with a 50-75 ml. gas bubble left in the bag maintained their pO₂ levels for the six day period.

Although the highest possible O₂ content may be desirable, in Trial #3, we experienced gas coming out of solution when the CPS, oxygenated at 4°C, was run through the CPS administration line. We noticed the gas in the line distal to the pinch clamp when the administration line was clamped after the OCPS had been infused.

We decided that the remainder of the testing and clinical trials would be with 100% O₂ added to the CPS at room temperature.

During Trial #4, we tested the room temperature OCPS with various amounts of undissolved gas left in the bag and then refrigerated over a two week period. Those 500 ml. bags that had an undissolved gas bubble 50-75 ml., maintained their pO₂ and O₂ content levels within 15% of the original levels for as long as two weeks. A gas bubble significantly larger than 75 ml. increased the pO₂>1000 mm Hg. when the CPS was then cooled to 4°C. This condition increased the risk of gas coming out of solution. Gas bubbles significantly smaller than 50 ml. could not maintain the desired oxygen levels for more than 2-4 days. If we saw a significant decrease in the size of the undissolved gas bubble, it could be shown that the oxygen level in the CPS had fallen to less than desired levels (<650 mmHg. pO₂ and <3.0 vol.% O₂ content). Additional oxygen can be added to the CPS bag with the depleted gas bubble to bring the bubble up to its original size. With proper mixing before use, this technique

will bring the oxygen levels back to the desired conditions.

We noted that there was no sedimentation or discoloration in the CPS bags. All components stayed dissolved in solution. The CPS bags tested maintained their sterility for the two week test period. There was a slight, but insignificant decrease in one component over the two week period (Lidocaine). The component degradation was not due to the presence of oxygen since the degradation also occurred in non-oxygenated CPS.

Discussion

From a literature review of CPS, there is sufficient evidence to support the use of high content oxygen in crystalloid cardioplegia solutions. For example, the depletion of ATP stores from the myocardial cells following a cross-clamp period supported by non-oxygenated CPS has been reported (5). The presence of high content oxygen in the OCPS should help to reduce the loss of ATP stores.

In order to add oxygen to the CPS effectively, we felt it necessary to modify our CPS solute content. The pharmacy added ionized calcium in trace amounts in order to avoid the reported "calcium paradox" that may occur during reperfusion (4, 12-14). Magnesium was added to help prevent intracellular calcium influx, potassium efflux, and to aid in myocardial oxygen metabolism (14,15). Mannitol was added to help reduce myocardial cellular swelling and to act as an oxygen free radical scavenger (especially for the OH⁻ ion), working to reduce myocardial cell damage due to metabolism by-products (16-18). We incorporated the 0.2µ Pall cardioplegia filter in the

Table 2

TABLE 2
OXYGENATION RESULTS
with
CARDIOPLEGIA SOLUTIONS

*** O ₂ mixture (before/after) results	100 % O ₂		95% O ₂ 5% CO ₂	
	OCPS Solution #1	Room Temp. Solution #1	OCPS Solution #1	Room Temp. Solution #1
Temp. during oxygenation	4 °C.	22 °C.	4 °C.	22 °C.
pH	7.626 / 7.691	7.683 / 7.742	7.554 / 7.360	7.688 / 7.501
pCO ₂ (mmHg.)	23.5 / 20.2	21.0 / 18.8	26.9 / 40.6	21.6 / 31.6
pO ₂ (mmHg.)	247.2 / 1280	239 / 806	199 / 1215	224 / 786
HCO ₃ (mEq./L.)	24.8 / 25.0	26.2 / 26.3	23.8 / 22.5	26.5 / 24.7
O ₂ CONTENT (vol.%)	1.16 / 6.01	1.12 / 3.79	0.93 / 5.71	1.05 / 3.69
Base Excess	-2.2 / -1.8	+2.9 / +4.1	+0.4 / -2.2	+4.0 / +0.9

*** The results shown with a slash (/) indicate results that were created (before / after) the oxygen mixture was added to the solution.

All OCPS gas results are uncorrected for temperature.

administration line to reduce the negative effects on the myocardium of the particulate matter in the cardioplegia perfusate (19-23).

When adding components to a cardioplegia base solution, the total volume of the base solution (including the estimated overflow) plus the volume of the added components should be considered when determining component concentration levels. If the added component volume and the base solution overflow are not considered in the component concentration calculations, the actual concentration levels of each component will be less than desired.

The addition of 100% O₂ in a static mixing condition at room temperature appears to achieve the desired O₂ content and acid-base balance. Even though adding 100% O₂ to 4°C CPS gave the highest oxygen content, we felt that the level of oxygen reached with room temperature OCPS gave us the safest mixture for a non-recirculating delivery system. The gas bubbles that came out of solution during Trial #4 in the 4°C CPS was probably caused by the instantaneous negative pressure imparted to the solution distal to the clamp by the sudden deceleration of the CPS, and the narrowing effect on the tubing as it is pinch clamped. The CPS bags oxygenated at room temperature, then cooled and administered at 4°C, did not have visible gas coming out of solution when the solution warmed back up to room temperature in the administration line. The lack of detectable gas bubbles in the room temperature solutions can be explained by the following: we mixed the CPS solution with gas at room temperature. When the solution rewarmed from 4°C to room temperature, it had returned to its initial equilibration point; therefore, the gas remained in solution.

The colder the solutions, the higher the degree of solubility of oxygen in that solution (Figure 2). Therefore, when the CPS that we oxygenated at 4°C warmed to room temperature, it warmed beyond its initial equilibration point, causing gas to come out of solution. The oxygen content of our OCPS (3.0 to 4.0 vol.%) may be sufficient to meet the oxygen requirements of the hypothermic arrested heart (1). This is, of course if the heart has been perfused and reperfused with the OCPS evenly and sufficiently to bring the myocardial temperature at least close to 10°C, and the myocardial temperature maintained at less than 20°C.

The key to maintaining the desired oxygen level in the CPS is leaving a gas bubble 50-75 ml. in the 500 ml. bag. Different sized CPS bags will probably require proportionately sized gas bubbles. Before priming the OCPS administration set, we remove the gas bubble from the bag. In our one year of clinical use, we have been able to maintain the pO₂ and O₂ contents of the refrigerated OCPS within 15% of its original values for at least two weeks.

With our simple delivery system, we can take a bag of OCPS out of a 4°C refrigerator and have it ready to infuse in less than two minutes. The use of preoxygenated CPS can be particularly

d. Abbott Labs, North Chicago, IL 60064

e. Baxter Healthcare, Deerfield, IL 60015

helpful in emergency cases. We use no cooling circuit or pump delivery system for OCPS administration; therefore, the cost of administering OCPS is less than \$50. With the need to contain or reduce the costs of cardiac surgery, this technique allows us to safely and effectively administer OCPS without the added cost and complexity of a pump delivery OCPS circuit.

A one to two week supply of CPS can be oxygenated at one time, and the bags can be stored in an upright fashion for up to two weeks, ready for use at any time. As we monitor the refrigerated OCPS daily, we have rarely found the need to reoxygenate the bags.

Concerning the type of bags used, we experienced great difficulty using the Abbott Labs 500 ml. bags (d) due to the tough, stiff membrane the administration line spike or filter spike is inserted through. The Baxter Healthcare 500 ml. bag (e) affords us a much easier and more secure insertion.

Pre-oxygenated CPS can be used not only in the delivery system previously described, but also may be applicable in a closed circuit pump delivery system not exposed to aeration of the CPS. The use of pre-oxygenated cardioplegia has become a simple, quick, inexpensive and effective method of myocardial preservation in our clinical setting.

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