CHAPTER 5 DISCUSSION

The problem that initiated the study was the fact that most infants who were undergoing hypothermic CPB encountered difficulties elevating $PaCO_2$ and pH using pH-stat management. There were several articles in various journals (Peter, 2002) that noted that CO_2 needed to be added to gas sweep of the bypass circuit to regulate pH-stat. We never had the same problem with adult cases that was undergoing hypothermic CPB. For this reason two hypothermic stage namely moderate and deep hypothermic bypass were investigated. Patients were not equally distributed according to hypothermic stages. Three different stages of analyses have been done to investigate the effect of carbogen intervention. Even though carbogen intervention was carried out only during cooling and the stable stage during cardiopulmonary bypass, analyses of data were performed for all stages as shown in Figure 3.4. Three separate graphs were plotted investigating whole CPB variable analysis (Table 4.3 a & b); $PaCO_2$ analysis during CPB (Fig. 4.3 a & b); $PaCO_2$ and pH analysis during cooling and stable stage (Fig 4.4 a & b). This is to quantify carbogen intervention at different stages and conditions in cardiac surgery.

Two distinct protocols for acid-base management are used in hypothermic cardiopulmonary bypass in clinical practice. Alpha-stat, arterial blood is measured at 37˚C, pH 7.40 and PCO_2 of 40 mm/Hg, whereas in vivo hypothermic blood is hypocapnic and alkalotic. In pH-stat, arterial pH and PCO_2 are maintained at constant values during cooling, such that pH-stat in vivo hypothermic blood revealed as of and pH 7.40, and the PCO_2 of 40 mm/Hg, and the arterial blood measured at 37˚C is hypercapnic and acidotic. Hypothermia, which is commonly used during CPB, can lead to decreased organ perfusion from vasoconstriction resulting, at least in part, from the reduction of the partial pressure of CO_2.

Baseline arterial blood gases in this study are not appropriate for use as a reference range because all infants are induced and intubated and ventilated before an arterial line is obtained. This may directly influence the baseline which could be considered as reference range in this study. Thorough studies have to be done to observe reference range of arterial blood gases in infant before any intervention is carried out. The reference range is universally accepted as a guideline for hemodynamically stable blood gases. When an intervention on $PaCO_2$ is carried out, it should be remembered that a $PaCO_2$ range that high is more difficult to correct with hyperventilation than low $PaCO_2$ which is easier to be corrected with ventilation or bicarbonate.

Clinically, if the starting point is a pCO_2 of 40 mm/Hg, a mathematical relationship can be shown. If the arterial pCO_2 increases by 20 mm/Hg, arterial pH will decreases by 0.20. If arterial pCO_2 decrease by 10 mm/Hg, pH will increase by 0.10. Alkalosis is present when the body has an increased pH: it is caused by either a respiratory or a metabolic factor. Respiratory alkalosis is caused by too much carbon dioxide being removed by the oxygenator on CPB and this is caused by excessive sweep gas to remove CO_2.

For this study, pCO_2 regulation was adjusted accordingly to gas sweep for control groups and gas sweep was kept at a minimum with additional intervention of carbogen for treatment groups. For each oxygenator (Capiox RX05 and Minimax Plus) the control and treatment groups to determine if carbogen intervention was necessary for an infant undergoing hypothermic bypass. Specifications of both oxygenators are shown in Table 5.1. Blood gas was corrected according to actual temperature of the patients, utilizing pH-stat management for both control (without carbogen) and treatment (with carbogen). The carbogen treatment was introduced to determine if we can overcome the problem of maintaining pH and PCO_2 for any infant undergoing

hypothermic bypass. Since the gas solubility increased with decreasing temperature, the partial pressure of CO_2 decreased, although the total content does not change.

Table 5.1: Specifications for Capiox RX 05 and Medtronic® Minimax Plus® hollow-fiber membrane oxygenators

Variables	**Terumo Capiox RX 05 (Baby RX)**	**Medtronic® Minimax Plus® Hollow Fiber Oxygenator**
Blood flow rate (L/min)	0.1 to 1.5	0.5 to 2.3
Reservoir	Hardshell narrow bottom	Hardshell broad bottom
Static priming volume (mL)	43	149
Reservoir capacity (mL)	1000	2000
Surface treatment/ coating	'X coating®' (PMEA-based polymer)	Minimax plus 3381 – without Carmeda Bioactive
Minimum reservoir operating level (mL)	15	150
Vacuum Assisted Venous Drainage (VAVD)	Applicable	Not applicable
Hollow-fiber material	Polypropylene	Polypropylene
Bundle Surface area	0.5 m^2	0.9 m^2
Oxygenator orientation	Horizontal	Vertical
Oxygenator & Reservoir	Integrated	Non-integrated

Hypocapnia, which results in alkalosis, has hazardous effects (Figure 5.1) on lung mechanics, cerebral blood flow, and the cardiovascular system. Both alkalosis and hypocapnia have been shown to increase pulmonary resistance and decrease lung compliance, which may lead to severe problems, especially in the weaning phase of CPB (Bayindir *et al.*, 2000; Coon *et al.*, 1975). In an isolated buffer-perfused lung model, Laffey *et al.* (2000) demonstrated that hypocapnic alkalosis is directly injurious to the lung and potentiates ischaemia/reperfusion induced acute lung injury.

Although cerebral oxygenation is autoregulated during cardiac surgery before and after CPB, it has been demonstrated that, during CPB, haemoglobin, temperature, pH, and pCO_2 determine at least 85% of all changes in cerebral oxygenation and the main causes of impaired cerebral oxygenation are a decrease in Hb with haemodilution, vasoconstriction due to hypocapnia, and leftward shift of haemoglobin binding curve in alkalosis and hypothermia (Nollert *et al.*, 1995).

Variations of $PaCO_2$ also affect systemic haemodynamics. It has been shown that hypocapnia ($PaCO_2$ = 30 mmHg) significantly decreases cardiac index by 9%, which has been associated with an inverse change in systemic vascular resistance index (Kazmaier *et al.*, 1998). Recently, Mas *et al.* (2000) demonstrated that acute hypocapnia ($PaCO_2$ from 41 to 34 mmHg) resulted in a significant increase in systemic vascular resistance and oxygen extraction ratio. In our study, $PaCO_2$ decreased significantly in both oxygenators (Capiox RX05 and Minimax Plus) control groups compared to treatment groups after initiation of CPB (cooling phase). Hypothermia and prolonged CPB time further aggravated these changes, and at stable phase, may produce nonphysiologic values in pCO_2 and pH. At the end of the rewarming period, with increased carbon dioxide production, pCO_2 values were elevated for both oxygenators regardless of either control or treatment groups.

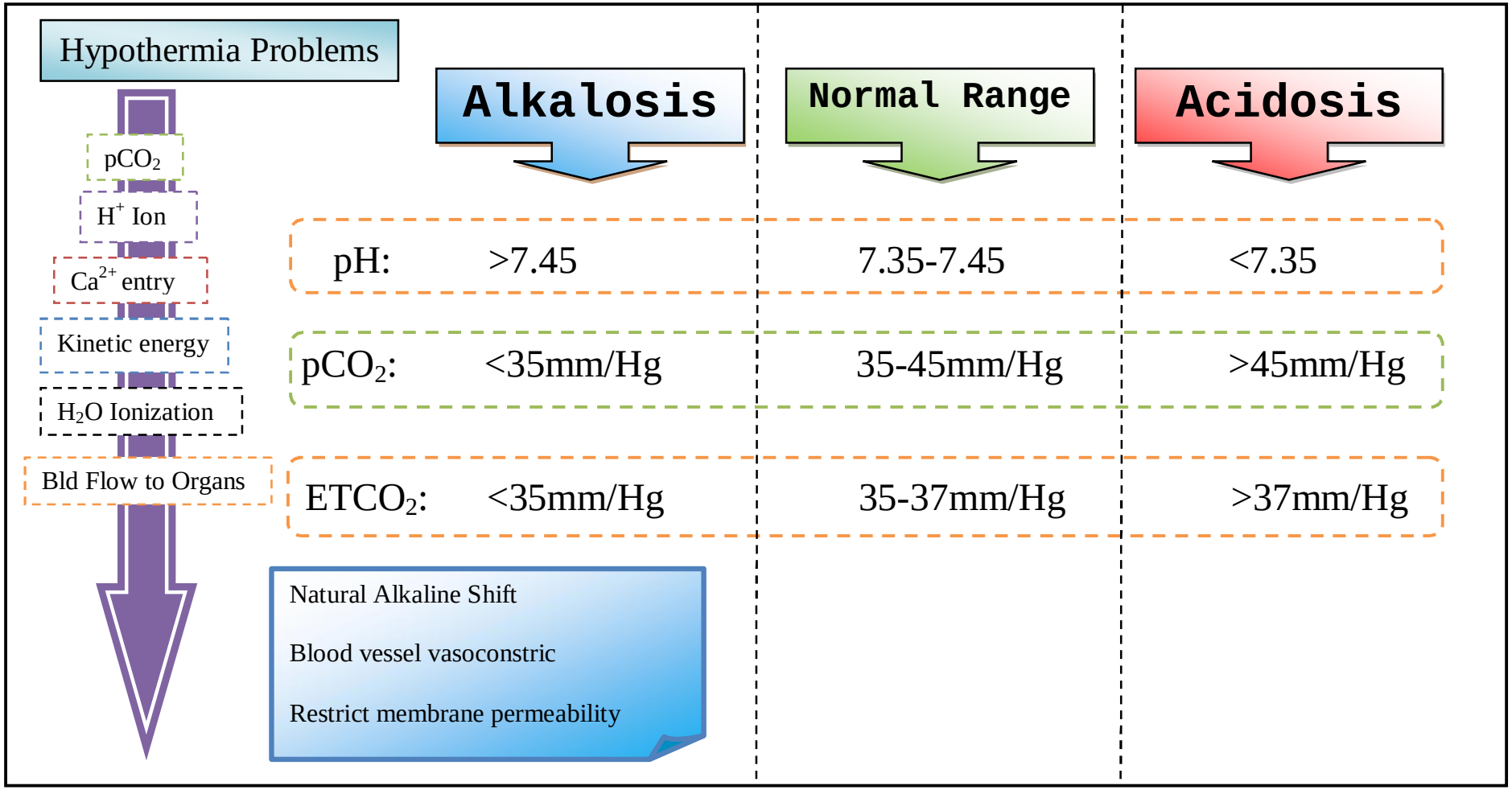


Figure 5.1: Hypothermia causes respiratory alkalosis.

The major limitation of this study is the use of a nonrandomized study design that could lead to bias in the patient's selection for to control and treatment groups. Although patients undergoing congenital heart disease correction (Figure 5.2) had similar baseline demographic characteristics within oxygenator group there was a difference in baseline between oxygenators. Federspiel and Hattler (1996) presented a simple analysis and graphic result for characterizing the effect of sweep gas flow rate on CO_2 exchange in artificial lungs. The analysis and its application require no detailed knowledge of the blood-side or membrane mass transfer characteristics; neither of the artificial lung device, nor of gas flow or blood flow pathways through the device. Neither does it require detailed mathematical or computer modelling of transport processes ongoing within the device. Rather, the analysis exploits a useful normalization to simply relate CO_2 exchange rate within artificial lungs to sweep gas flow rate, independent of device specific flow and mass transfer complexities. Thus, although a specific model oxygenator was used, recommendations for sweep rates obtained from this study may be universally applied to all membrane oxygenators.

Indeed, haemoglobin buffers the hydrogen ions produced by CO_2 hydration to bicarbonate and directly combines with some CO_2 to form compounds of a carbamino type (Roughton, 1964). Haemodilution also decreases blood capacity for transporting both O_2 and CO_2 (Cavaliere, 2000).

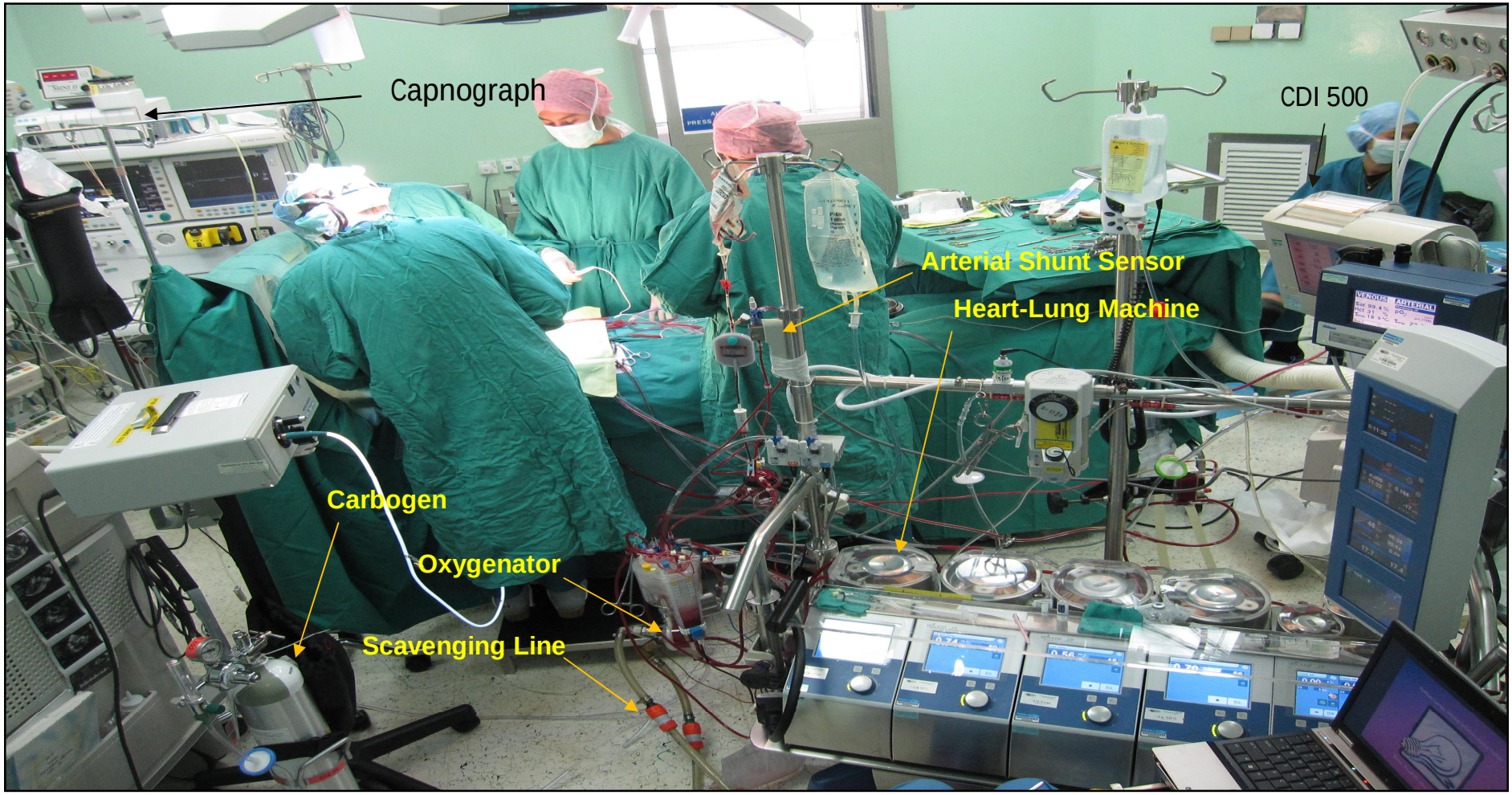


Figure 5.2: Operation theatre arrangement for open heart surgery with carbogen treatment.

5.2 Paediatric cardiac surgeries

Paediatric cardiac surgery involves several stages from preparing the patient to the intensive care after the surgery. Firstly the, patient is given a premedication and an intravenous anaesthetic just before the operation. When patient is unconscious, intubation and ventilation is performed. Secondly, the transoesophageal echocardiographic (TOE) probe insertion into patients on surgical table is performed. TOE is a flexible tube, about the width of a finger, with a small ultrasound probe on the end. With correct placement, it allows visualization of the structure of the heart. Third stage involves the surgeon, as he cuts through the patient's breastbone to gain entry to the thorax. This enables direct access to the heart after exposing the pericardium. By the fourth stage the patients heart is cannulation. Once the pericardium has been opened the surgical team cannulates the aorta and right atrium for many of the cases and connects patients' heart to the heart-lung bypass machine. Different surgical team performed a variety of surgeries for individual cardiac diagnoses. The fifth stage involves cardiopulmonary bypass monitoring to ensure properly maintained circulation and oxygenation of patients' blood. During this period the surgical team will perform the surgical correction to the heart. Sixth stage is final phase whereby ventilation, intensive care and recovery take place (Figure 5.3). Postoperative care was provided in the paediatric intensive care unit (PICU), with management provided by members of paediatric cardiology, paediatric critical care nurses, and cardiothoracic surgery staff. Currently patients were monitored continuously with Philips software called Intellivue Clinical Information Portfolio (ICIP) System. This is a computer-based system linked to a central monitoring station but for this study manual data collection has been utilized.

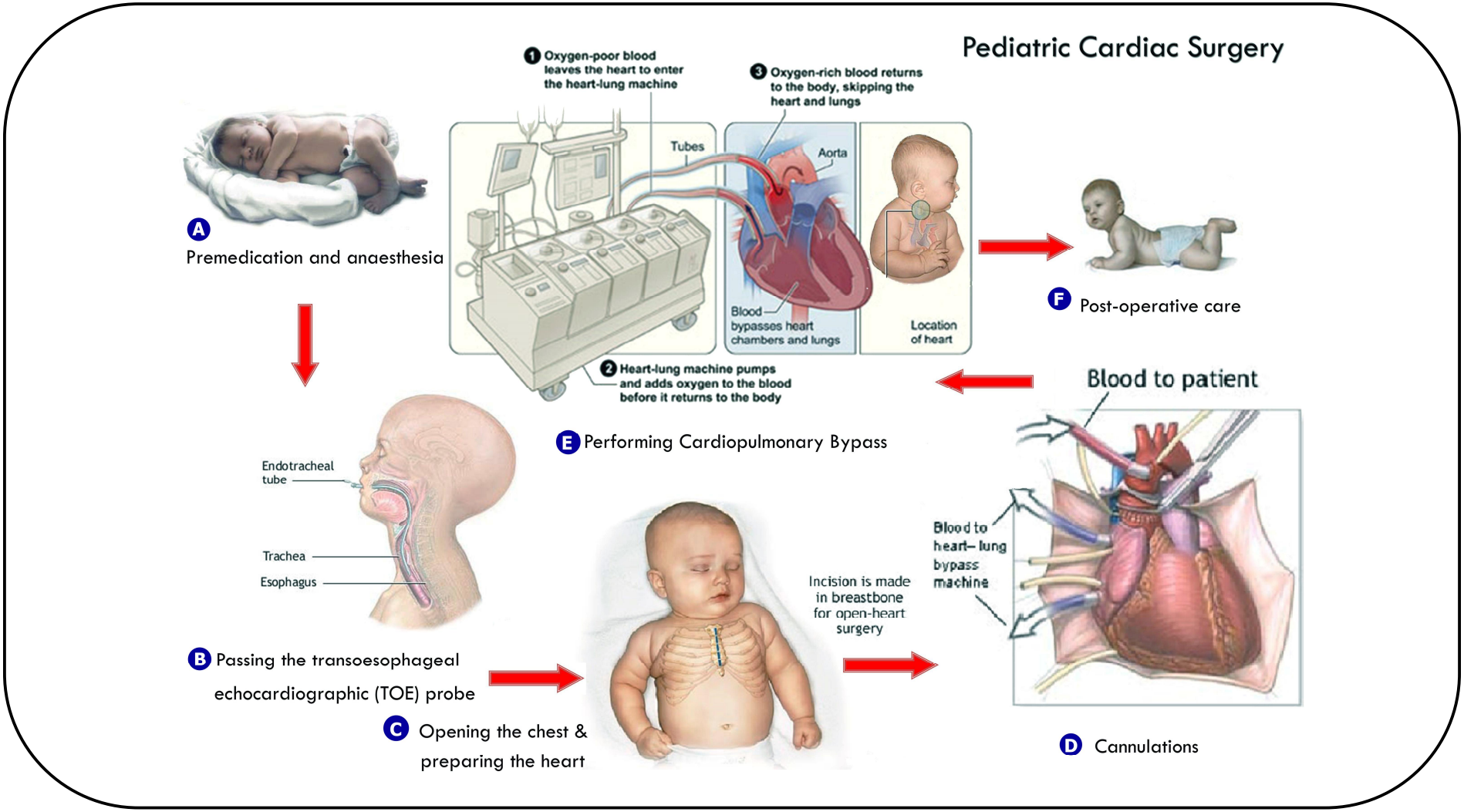


Figure 5.3: Paediatric cardiac surgery. A: Premedication and anaesthesia; B: Passing the transoesophageal echocardiographic (TOE) probe; C: Opening the chest and preparing the heart; D: Cannulations; E: Performing CPB; F: Post-operative care

5.3 Limitations and comments

Oxygenators' evolution began with using lung as natural gas exchange through ventilation support to the lung. Evolution of oxygenator began with the invention of bubble oxygenator and led to the modern membrane oxygenator. A membrane oxygenator can be divided into microporous polypropylene (0.3 to 0.8 μm pores) or silicone rubber oxygenator at current generation. Although this study was randomized controlled trial, there are some limitations. Firstly, ventilation through a GA machine is vital for the patients in the operation theatre. Typically, arterial blood gas (baseline reading) will be performed after ventilation is secured in infant. An ABG performed after ventilation is to evaluate oxygenation adequacy. There are differences between ventilated patients and natural atmospheric breathing patient which could lead influence the pCO_2 reading during baseline ABG. It is therefore important to obtain ABGs from ventilated infant patient before, during and after bypass. Meanwhile during bypass, minimal ventilation is performed by the anaesthetist to prevent atelectasis or "collapse of the patients' lung" after the bypass is terminated. Air and O_2 are insufflated in different ratios depending on anaesthetic decision. This minimum ventilation to infant's lung might influence pCO_2 content in patient's blood but the influences of it are not significant for this study. Sometime, a hyperventilation intervention is applied to decrease entidal CO_2 before or after cardiopulmonary bypass. A few post-CPB cases that received hyperventilation might or might not be related to carbogen treatment. Further study in this matter should be continued to answer the questions raised.

Length of the surgery may vary according to cases. In some cases, surgeons are required to go back on CPB several times depending on the diagnosis of TEE or readings on blood pressure of particular blood vessels. This might in turn affect ABG results, create electrolyte imbalance, reperfusion injury, lung injury, etc. Furthermore, surgeons who perform different methods of surgical correction from the case may cause

the length of the particular surgery to be prolonged and in turn influences CO_2 build-up in body of the patient. Cases with bypass time less than 60 min do not affect ABG result especially during cooling or stable period. This situation is almost frequently seen in mild hypothermia patient when the surgery is short.

Patients' body temperature can be distorted by a few factors in the operation theatre. This includes operation theatre temperature, absence of humidifier with heating element, body surface area and time duration for chest closure. Additionally, nasopharyngeal temperature with temperature probe inserted in nasal cavity of an infant, may be affected by ventilation via GA machine without a heated humidifier. This situation causes both pre and post bypass temperature to drop by 2 to 5˚C despite the use of bed warmer or blower for some cases. Pre-operative or baseline nasal temperature may vary from one infant to another. Pre-operative ABG were performed with the normal body temperature of an infant assumed as 37˚C. This is because nasal temperature probe is inserted later than arterial line insertion. ABG results during surgery should be based on arterial line temperature (on heart-lung machine) rather than patients' nasal temperature for accurate ABG reading. Duration of CPB cooling varies between cases, contributing to pCO_2 regulation in patients and carbogen usage. Hypothermia increases the solubility and affinity of oxygen and carbon dioxide. During rewarming on bypass there was an increase in cerebral fraction oxygen extraction (FOE) only in patients who had a continuous flow bypass (SP Wardle *et al*., 1998). In this study carbogen treatments are stopped during rewarming. Moreover, CO_2 production is higher during rewarming and therefore caution must be used not to hyperventilate the patient which may lead the patient to hypocapnia.

Carbogen treatment causes a few problems, interms of setting-up and delivery. Setting-up the carbogen requires extra time beside the normal check-up and priming of CPB machine. Moreover, pO_2 level during CPB easily reaches more than 600mm/Hg

even if FiO_2 adjusted at 21% because carbogen has been delivered at 1L/min (Table 5.2).

Table 5.2: Advantage and disadvantage using carbogen to treatment of pH-stat management during hypothermia.

Carbogen Usage During CPB	
Advantage	**Disadvantage**
pCO_2 level elevated at any gradient temperature	High pO_2 level
Dilates vessel during hypothermia (cerebral oxygenation increase)	Expensive
Increased pH level caused by respiratory alkalosis are treatable	Consumes time for set-up
	Occupies extra space
	Need titration
	Extra monitoring devises have to be applied to monitor carbogen intervention

This phenomenon might influence hyperoxemia or oxygen toxicity. PCO_2 level is elevated together with the elevation of PO_2. Hyperoxemia has adverse effects such as the presence of reactive oxygen species. These endogenous antioxidants cause cellular damage. At the same time it has also been used to reduce nitrogen bubbles (Justin, 2006). Air blenders are kept at a minimum FiO_2 of 0.2 and gas sweep at 0.1L/min in order to flush in sevoflurane from circuit to the oxygenator. Generally, the higher the pump flow the greater the oxygenator's capillary area, the more carbogen is used. Excessive gas flow may cause low pCO_2, alkalosis, or blood damage (Terumo

Cardiovascular Systems; 2003). Carbogen is an expensive gas. It has to be prepared with oxygen (95%) and carbon dioxide (5%), and stored in cylinders of capacity 1.4m^3/10L. The usage depends on flow, bypass time (cooling to rewarming period) and surface area of the oxygenator's fiber. Carbogen usage may also vary depending on the length of surgery or the temperature that patients have to be cooled to: mild, moderate or deep hypothermia. In addition, we personally had difficulty with carbogen supply as the factory which produced them had a technical problem causing a delay. There were a few cases which were in the treatment group but the pCO_2 readings were constantly in normal range during CPB and needed no carbogen usage.

The infant's small body size and immature thermoregulation sensory receptors development challenge CPB being performed on them. There are also anatomical problems of the congenital heart. Furthermore, the heat loss from an infant is faster than in adult. BSA of an infant is small and this causes a lesser CO_2 production, in comparison with an adult who can produce reasonable CO_2 for compensation. Gas sweep that is integrated with heart-lung machine is not sufficient to increase the CO_2 level even if gas sweep are decreased to a minimum level (0.1 l/min).

Perfusion techniques may vary from one to another perfusionist. Priming solution usually contain Plasmalyte, Albumine 20%, Mannitol 10%, Packed cell (1 unit), and sodium bicarbonate and other drugs. Perfusionist should balance this priming solution in the circuit at the onset of the surgery by correcting electrolyte and gases according to blood's normal range by performing an ABG investigation before going on bypass. CPB influences CO_2 production in patients' body by a few factors; haemodilution, hemofiltration, hyperperfusion or overflow into patient circulation. Usage of Phenylephrine as a vasoconstrictive agent might restrict CO_2 exchange, intra or extracellular. CO_2 flush is not applied for this study even though it is recommended for both oxygenator before priming. The aim of CO_2 flush before priming is to make it easy

for de-bubbling macro and micro air from the circuit. Nevertheless, we practice warming-up the heat exchanger to 36˚C during priming to de-bubble properly before surgery.

Capnograph is a device used to evaluate mean CPB pump expired carbon dioxide ($peCPBCO_2$) through oxygenator gas outlet. FiO_2 and gas sweep adjustment alter capnograph reading [$peCPBCO_2$ (mm/Hg)]. $peCPBCO_2$ decrease when FiO_2 increase and vice versa. There is an isolated incidents where the capnography reading showed 8 to 9 mm/Hg $paCO_2$ but the ABG showed pCO_2 = 30mm/Hg during or just into rewarming stage indicating a possible ventilation perfusion problem. Scavenging line outlets are vulnerable to water condensation, as the exhaled air are cooled and are warmed-up in a heat exchanger before passing through the capnography to measurement of $peCPBCO_2$. These water condensation alter the $peCPBCO_2$ reading and block the air passing through. Caution is taken to prevent the water blocking the capnography reading. Scavenging line is also susceptible to be stepped on or wheeled over. This can prevent wall suction and reading from capnography may drop for the period the line is kinked or stepped on (Figure 5.4). From the observation, haemodilution decreased end-tidal CO_2 immediately. Time is required for the machine to capture the carbon dioxide from the oxygenator gas outlet. In some case a few minute are required for accurate reading of the machine. Thus there is a debate on parameter to use: End-tidal CO_2 or blood gas measurement. End-tidal CO_2 measured through capnography is a more economical way to monitor CO_2 from exhaled gas from patient or oxygenator. It is recommended however to use blood gas monitoring device such as inline monitoring CDI 500 or ABG machine (Cobas b 211 system) to confirm blood gases. There are few other problems faced by perfusionist during the handling of the heart-lung machine with the accessory machinery required during this study. Difficulties include the handling of different types of ABG machine. The machines in

used are Cobas b 221 system, Roche Diagnostics; ABL 700 series, Radiometer Copenhagen; CDI^{TM} 500 Blood Parameter Monitoring Systems, Terumo Cardiovascular Systems, USA; and i-STAT$^{®}$ 1 Analyzer, Abbott, East Windsor, NJ, USA: using CG8+ cartridge which may alter the ABG result. CDI 500 system is an in-line blood gas monitoring device which has been used in this study for monitor and adjustment of carbogen delivery and allows a continuous measurement of PaO_2, $PaCO_2$, pH, K^+ and temperature as well as haematocrit, haemoglobin and the saturation of haemoglobin in venous blood (Svo_2). But, there are a few problems noted during usage of CDI 500 system. The most obvious observation is in the actual temperature measurement that might be influenced by heat loss from monitoring line connected in and out of arterial shunt sensor. Moreover, using CDI 500 system in infant circuit causes extra-shunting in ECC circuit but this is balanced by the availability of electrolyte and blood gases analyse.

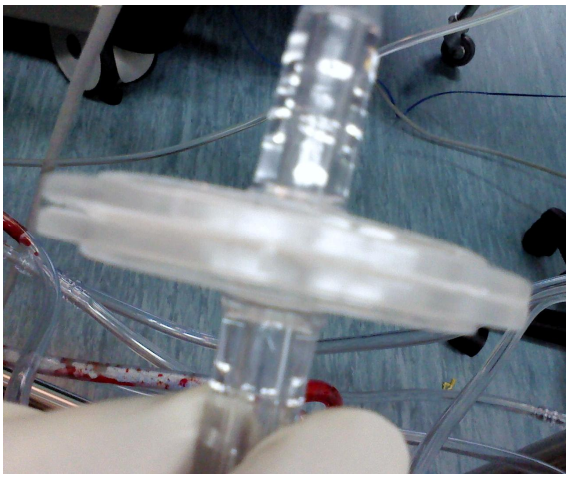
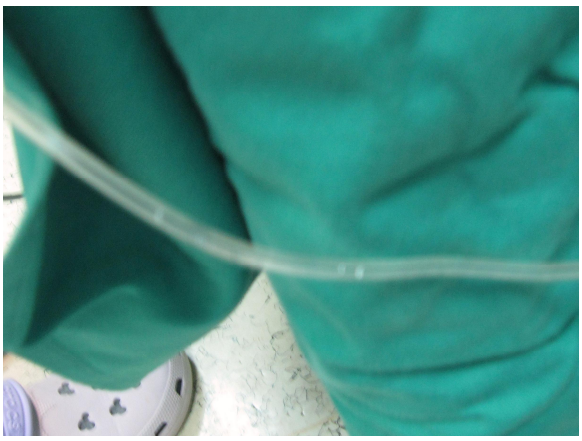
	
Defect's in ¼ tubing filter at critical gas supply line restrict delivery of desired gas to oxygenator.	Scavenging line has to be secured along the line to prevent accidental stepping on the tubing or kinks caused by instruments.
	
Water condensation through-out line connecting exhaust gas outlet from oxygenator to capnography may alter peCPBCO_2 reading at GA machine.	Wall suction should always be checked when scavenging line is in use to prevent false positive result.

Figure 5.4: Common troubleshooting that happens during carbogen treatment.

Even though the shunting is small, but in combination with other shunts such as hemofiltration, the sampling line may cause a drop in ABP of patient. To counter-act this situation, perfusionists have to increase the flow of the main pump. CDI 500 system does not have Na^+, Ca^{2+} and glucose parameter measurements, which have to be confirmed by regular ABG machine, before, during and after cardiopulmonary bypass. The length of time to perform ABG analysis and bubble formed in syringes containing patients' samples may influence ABG result. Minimal values of FiO_2 and gas sweep have to be determined to get adequate sevoflurane delivered to patients' blood. Currently, carbogen is connected after the gas blender and sevoflurane outlet. Full utilization of carbogen may be strategically located to maximize sevoflurane usage as well. An isolated incident happened when the O_2 line tubing which contained filter leaked out air, before passing into the oxygenator and preventing accurate gas delivery. The oxygen line tubing filter, which filters out any micro-particle from gas line may have cracks, or are not well sealed. These human error or manufacturing faults may cause air, O_2 and anaesthetic gas to leakage before reaching the oxygenator.

A few questions arose during the period of this research. Firstly, how does the metabolism of $NaHCO_3$ influence pCO_2 in patient's blood? Secondly, in this research we observed that patient's blood pressure had a relationship with pCO_2 of patient and further studies should be done to optimize the correlation. The condition whereby the pCO_2 reached optimum level the blood pressures increased or optimized for paediatric case are noted. Thirdly, all measurements are based on extracellular CO_2. What is the influence of intracellular CO_2 on patient's metabolism? Fourthly, CO_2 production versus consumption is patient related. Various factors influence CO_2 production and consumption in general. Examples of these various factors are temperature, oxygenation, full flow and gas blender adjustment. The present study is limited by the fact that no measurements were performed in the late phase of CPB to investigate

whether these observations are time related and/or whether they persists into intensive care period. Finally, oxygenator position or alignment may affect gas exchange according to gravitational force which may need further depth study. For example between the two groups of oxygenator that were being studied Capiox RX05 had a horizontal position while Medtronic Minimax had the vertical oxygenator position. A few cases that were noted that did not required carbogen as treatment to elevated the pCO_2. These cases have pCO_2 level normalized through-out the CPB. Careful note on circumstances that provided the condition would have been needed.

Observation showed that ABP of the patient have a relationship with fluctuation of pCO_2 level during CPB. A more comprehensive study should be performed to evaluate the relationship between ABP and pCO_2 for patients undergoing open heart surgery. If a normal range of pCO_2 achieved, in blood ABP desirable ABP can be recorded. There is pressure difference between body of a bypass patient and diver's. There is a possibility of using a technique of re-breathing for longer CPB time according to temperature (with specific air recycler and utilize air and oxygen sufficiently). Another area of advancement that could be considered is a nanobiotechnology breakthrough in development of membrane fiber oxygenators to support maximum gas exchange. A temperature auto-regulation of blood gases might be achieve by integrating towards membrane oxygenator to improve patients outcome in the future. Rather than integrations between oxygenator and arterial filter in current generation, option should be explored for intelligent fiber material that self-correct blood gases according to temperature and overcome clot formation from drug interaction. Given the nature of the underlying heart disease, the need for expedience, and the fact that existing heart failure may confound the outcome of the study which limits further evaluation of postoperative outcomes.

CHAPTER 6 CONCLUSIONS

From the present study, we conclude that carbogen usage improves the percentage of $PaCO_2$ and pH level falling within the reference range as compared to control group. Sweep-gas flow adjustment alone would not be sufficient to control $PaCO_2$ during all phases of CPB for paediatric patient. For this reason carbogen intervention is helpful to regulate $PaCO_2$ as treatment group during CPB at moderate and deep hypothermia for both types of oxygenators. Results on oxygenators show that Capiox RX05 is more carbogen dependent than Minimax Plus. Furthermore, this study provides a better understanding of the relationship between temperature gradient and carbogen usage to regulate pCO_2 and pH during CPB. It is hoped to be present study provides an avenue for future investigations into the efficiency of carbogen usage during CPB according to age group and temperature gradient can be done in randomized control trial manner.