33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

Cold Intermittent Cardioplegia Reduces the Acidosis During Prolonged Cardiac Surgery with Cardiopulmonary Bypass

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Abstract— **The effect on acid-base balance efficacy of intermittent warm and cold blood cardioplegia (IWBC, ICBC) was assessed in 44 patients who underwent cardiac surgery with prolonged aortic cross clamping. With this purpose a customized multi sensor probe was inserted in the coronary sinus, and pH, PO_2, PCO_2 and temperature were continuously measured at 1 Hz sampling rate. The mean cross-clamping time was of 76 ± 26 min on 19 IWBC cases and of 80 ± 24 min on 14 ICBC cases. With IWBC perfusion, at the end of every ischemic period, the lowest pH and PO_2 progressively decreased and the maximal PCO_2 increased. During ICBC the minimum of pH and PO2 and maximum of PCO2 at the end of different ischemic period during time were constant, also during long cross-clamping time. With IWBC, myocardial ischemia seemed not completely reversed by standardized reperfusions, as reflected by steady deterioration of PCO_2 and pH after each reperfusion.**

I. Introduction

THE use of cardioplegia to achieve the ideal conditions for cardiac surgical operations was introduced over 40 years ago in clinical practice [1]. After a first phase in which continuous cardioplegia was performed as a physiological approach to myocardial protection, intermittent delivery has been proposed as an equally effective and more practical technique [2]. While the use of oxygenated potassium-enriched blood solution for reducing electrochemical activity and consequently oxygen demand has been widely adopted, the optimal temperature of intermittent blood cardioplegia to obtain the best preservation is again controversial [3,4].

Although oxygen consumption is reduced by potassium cardioplegia, myocardial acidosis may be still developed by cardioplegic arrest that in turn produces local red cell acidosis with a shift to the right of the oxygen haemoglobin dissociation curve. Further, as the demand of oxygen is higher with temperature increasing acidosis may be facilitated by myocardial warming. However, hypothermia may have adverse effects like inhibiting the Na-pump to cause oedema and shifting of the oxygen-haemoglobin dissociation curve leftward [5].

Many clinical methods, mainly based on serial collection of the myocardial specific biomarkers or myocardial tissue assay, has been used to assess myocardial metabolism during cardiac surgery for quantifying the degree of physiologic impairment at various stages of cardiac operation and assess perfusion safety [6]. Among those pH and acidosis state seem assume a relevant role as indicator of myocardial distress [7].

The possibility of assessing adequacy of myocardial preservation by continuous measurement of intramyocardial tissue pH in man has been early demonstrated by Khuri and successively clinically introduced [8,9]. Recently, an innovative technology for continuous measurement in the coronary sinus of blood gas parameters has been proposed for accomplishing a control system of myocardial protection during cardiac surgery with prolonged cross-clamping time [10]. The on-line monitoring of pH, PCO_2, PO_2 and temperature of myocardial refluent blood, was possible by inserting a probe in the coronary, thus providing a measurement of acidosis time course as on line marker of efficacy of myocardial protection. The introduction of above reported methodology make now possible to bring new knowledge on the potential beneficial effect of hypothermia in preserving myocardial metabolism during intermittent blood cardioplegia.

Hence, the aim of this study was to compare the effect on acid-base balance efficacy of intermittent warm and cold blood cardioplegia (IWBC, ICBC) by monitoring in patients myocardial acidosis during cardiac surgery with prolonged aortic cross clamping.

II. Materials and Methods

A. Patient Selection

During a period of 30 months, patients undergoing cardiac surgery with extracorporeal-circulation were selected for continuous intraoperative monitoring acid-base status. The study was conducted only on patients with expected long cross-clamping time with at least four cardioplegia doses.

A total of 44 patients were included and operated on with cardiopulmonary bypass at 34–37°C: 25 patients were perfused with IWBC 34°C and 19 patients with ICBC 10°C. Mean age of patients was 66 ± 10 years (25 males).

B. Intraoperative Monitoring

The continuous intraoperative measurement of myocardial acid-base condition was achieved by the multi sensor

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Paratrend® 7 linked to the Trendcare Continuous Blood Gas Monitor (Agilent Technologies). The Trendcare™ monitor and Paratrend® 7 sensor are medical devices designed for close monitoring of blood gases in a critical care or surgical setting of paediatric or adult patients who require ventilation [11,12].

For the intraoperative use the probe was customized to be inserted in the coronary sinus in sterility condition and to maintain stable position during surgery manoeuvres [10]. The probe had an external diameter of 0.50 mm, a micro porous polyethylene tube covered it and in the tip part were enclosed four sensing elements: pH, PCO_2, PO_2 sensors based on fiber optic and a thermocouple as a temperature sensor. The pH sensor is founded to the principle that an indicator dyes change colour when exposed to hydrogen ions. Phenol red is used as indicator dyes and immobilised in an ion-permeable gel in the tip part of the probe. The sensing elements is surrounded by a micro porous hollow fibre warranting that the hydrogen ions of the blood permeated through the gel and caused the dye to change colour. The indicator absorbed the measuring beam (wavelength 555 nm) and so the change colour of the dye is related to the hydrogen ions concentration. PCO_2 sensor is based on the same principle as the pH sensor, but the indicator dye contains sodium bicarbonate and phenol red indicator. Carbon dioxide is allowed to pass through and reacted with the sodium bicarbonate to release hydrogen ions that reacted with the dye to cause it to change colour. PO_2 measurement is based on the principle of fluorescence quenching by means of oxygen sensitive indicator dye immobilised in a gas permeable silicon rubber complex. The measuring beam (wavelength 460 nm) is transmitted down the optical cable, absorbed by indicator dye and fluorescent light emitted. In the presence of oxygen, the fluorescent light is quenched. The temperature measurement is based on a thermocouple: a copper constantan junction generates a voltage which is a function of temperature.

The three parameters are continuously measured with high precision assured by Paratrend® 7 sensor: 0.01 pH unit, 0.1 mmHg PCO2 tension, 1 mmHg PO2 tension and 0.1 °C. The Trendcare Continuous Blood Gas Monitor is a microprocessor-based device directly linked to the probe, which administered the sensor calibration and warranted moreover, optical and electronic signals digital data conversion, continuous data display, print and transfer by RS232 to a Notebook.

C. *Surgical Management*

Data were acquired and stored at a rate of one sample per second. Intermittent blood cardioplegia was performed as described by Calafiore et al. [8]: induction with a three min dose of 300 cm^3/min oxygenate blood with a potassium bolus of 6 mEq and a concentration of 20 mEq/l, maintenance with two min dose of 200 cm^3/min oxygenate blood every 15-20 minutes with a potassium concentration of 16 mEq/l. Maintenance was obtained with 2 min doses, injection rate of 200 cm3/min, given every 10–20 min, and a potassium concentration of 16 mEq/l.

Maintenance doses were administered antegradely or retrogradely in coronary artery patients and retrogradely in aortic valve patients. The coronary sinus was in both cases cannulated through the right atrium. In mitral valve patients, maintenance doses were administered retrogradely, with the cardioplegic cannula directly inserted in the coronary sinus and secured by means of a purse-string suture. In every intervention the sensor was previously calibrated, the patient was cannulated for the extracorporeal-circulation activation and the cardioplegic cannula was directly inserted in the coronary sinus and secured by means of a purse-string suture, the cross-clamping was induced and finally the Paratrend® 7 covered by a sterile sheath was linked to the cannula by a Y connector. To the other side of the connector was linked the cardioplegia delivery line. The probe tip was moved forward 4 cm out of the coronary sinus cannula directly in contact to the refluent myocardial blood. Finally, the correct position of the sensor and his contact with blood was checked by manual palpation and confirmed visually by checking of data acquisition.

D. *Data Processing and Statistical Analysis*

The acquired data were processed by removing artifacts brought about by fiber optic pleat and/or overexposure and by calculating the descriptive statistics parameters as the means ± the standard deviation. Wilcoxon Mann-Whitney test was used to compare intra-group means.

III. Results

Due to breaking during probe insertion in the coronary sinus, the continuous measurement was not possible in all cases. A subgroup of 36 patients out of 44 was eventually monitored. On average the mean cross-clamping time was 76 ± 26 minutes on the 19 IWBC cases and 81 ± 23 minutes on the 17 ICBC cases (see Table 1 for demographic characteristics).

TABLE I
Patients Demographic Characteristics

	IWBC	ICBC	Total
Patients	19	17	36
Male	15	10	25
Female	4	7	11
Age	65±8	64±12	66±10
CABG	5	-	5
Valve	6	7	13
CABG+Valve	8	8	16
Others	-	2	2

IWBG: intermittent warm blood cardioplegia; ICBC: intermittent cold blood cardioplegia; CABG: Coronary Artery Bypass Graft.

In IWBC group the mean perfusion time per dose was 2.3±0.3 minutes, and mean ischemic time between doses was 13.0±0.2 minutes, instead in ICBC group the mean perfusion time per dose was 1.9±0.2 minutes, and mean

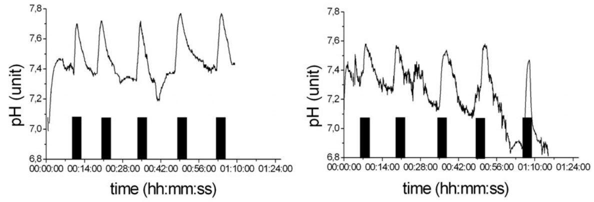

Fig. 1. pH value trend during cold (left panel) and warm (right panel) intermittent cardioplegia.

ischemic time between doses was 14.2±1.4 minutes. All patients received at least two cardioplegia doses, 33 received three doses, 21 received four doses, 11 received five doses, six received six doses, and finally two received seven doses.

The temperatures at the end of every ischemic period during IWBC and ICBC protocols resulted no significantly different and equal to 32.4±1.7 and 32.7±1.1 °C. As previously shown [10], blood gases showed a common pattern characterized by the rise of pH during perfusion time, fall during ischemic period and by the fall of PCO_2 during perfusion and rise during ischemic period. The general pattern of PO_2 showed a contextual rising of tension with the coming of the oxygenated blood followed by a monotonic decrease during ischemic period.

In Figure 1 the typical pH value time course during complex surgery with prolonged cross-clamping time was displayed for an ICBC and an IWBC patient. Although the general pattern of acid-basis status was the same, ICBC revealed different results as pH level during ischemic time seems preserved. Differently, IWBC patient showed a progressive decrease of pH values at successive clamping period.

For comparative analysis the pH values were referred at the temperature of 37°C. The pH reached a minimum at the end of every ischemic period that decreased progressively along with the IWBC protocol. As showed in the Figure 2, pH moved from 7.30 ± 0.18 at the end of the first period to 7.21 ± 0.15 at the end of the second, to 7.11 ± 0.18 at the end of the third and to 7.08 ± 0.18 at the end of the fourth.
On the contrary, in the ICBC protocol, pH reached at the end of every ischemic period was constant and significantly higher being respectively 7.28 ± 0.17 (p=0.8), 7.30 ± 0.13 (p=0.036), 7.28 ± 0.15 (p=0.003) and 7.21 ± 0.14 (p=0.046). In the subsequent (fifth) dose the pH values were respectively 7.09 ± 0.13 in the warm protocol and 7.24 ± 0.10 units in the cold protocol (p=0.048). Probably due to the small simple size, the difference between the two protocols resulted no significant in the sixth ischemic period (p=0.13). On the whole, minimum pH values were 7.10 ± 0.17 and 7.24 ± 0.07 (p <0.025) respectively in IWBC and ICBC groups.

Measurement of PCO_2 and PO_2 resulted less reliable as specific probes failed in several cases thus reducing or inhibiting statistics for higher cardioplegia doses. However some relevant findings should be reported for PCO_2.

The maximum value achieved by rose in both protocols

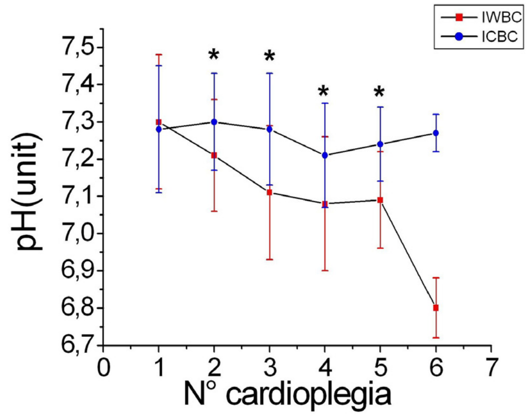

Fig. 2. : minimum values of pH achieved at the end of subsequent ischemic periods.

TABLE II
PCO_2 VALUE AT THE END OF EACH CLAMPING TIME*

	ICBC	IWBC	P
1	37.8 ± 10.8	53.3 ± 13.8	0.002
2	39.3 ± 10.5	54.9 ± 11.8	0.003
3	41.4 ± 8.8	64.7 ± 25.1	0.020
4	49.0 ± 10.2	64.1 ± 13.4	0.046
5	46.1±9.9	95.4	-
6	48.7±5.8	-	-
7	52.4	-	-
8	57.5	-	-

*: Due to probe fault the some values were not available.

TABLE III
PO_2 VALUE AT THE END OF EACH CLAMPING TIME*

	ICBC	IWBC	P
1	45 ± 55	43 ± 48	0,7
2	41 ± 33	46 ± 50	0,9
3	45 ± 48	49 ± 51	0,5
4	34 ± 26	38 ± 21	0,5
5	42 ± 31	-	-
6	21 ± 12	-	-
7	31 ± 16	-	-
8	-	-	-

*: Due to probe fault the some values were not available.

during the subsequent perfusion-ischemia phases. However as reported in Table 2, maximum of PCO_2 at the end of different ischemic period showed different behaviour in ICBC and IWBC patients. On average, in the ICBC group maximum of PCO_2 doesn't exceed 50 mmHg and resulted always significantly lower than in IWBC group. During warm protocol PCO_2 reached 64 mmHg at the fourth ischemic episode, with a trend of successive increase. Differently, no significant differences were elicited in PO_2 behaviour during warm or cold protocols (Table 3).

IV. Discussion

The duration of cardio pulmonary bypass is known to be an important predictor of outcomes of open-heart surgery [13] Long cross clamping duration has been related to the degree of systemic metabolic acidosis [14], and myocardial tissue acidosis in turns has been associated to postoperative adverse outcome and increasing of cost of care [15]. Thus, optimal intraoperative myocardial protection till remain an important task to improve postoperative adverse outcome and reduce cost of care. After introduction of blood cardioplegia a variety of methods have been proposed and are still subject of investigations to improve its protective effect in open heart surgery. Among those, main efforts have been directed to enrichment of the solution with metabolically active ingredients or trimming of delivery modality by changing pressure, time and temperature of the cardioplegic solutions.

Different temperature of cardioplegia administration has indeed a significant impact on the metabolic activity of the heart, thus suggesting to protect myocardium from ischemia by reducing cardioplegia temperature [5]. However this approach is still controversial and debated [16].

The possibility to in-line monitor blood tissue acidosis offers an intriguing possibility to verify myocardial suffering during aorta cross clamping [6, 10, 15, 17]. In this work the effect cardioplegia temperature on myocardium protection was assessed by continuous measurement of blood pH, carbon dioxide, and oxygen tension of the coronary sinus blood during open heart cardiac surgery. We assumed that blood gases at the coronary sinus reflected directly and globally, the exchange of gases between myocardium and coronary vessels blood thus representing a reliable index of myocardial tissue acid-base balance.

In our patients, blood gases variations during ischemia-reperfusion phases showed different pattern depending on warm or cold cardioplegia administration was applied. With IWBC, pH and PO_2 progressively decreased and maximal PCO_2 increased at the end of every ischemic period. Conversely, with ICBC protocol the minimum of pH and PO_2 and maximum of PCO_2 at the end of different ischemic period during time were constant, also during long cross-clamping time. Thus, IWBC seemed inadequate to protect myocardium during long lasting open heart surgery. Myocardial ischemia seemed indeed not completely reversed by standardized reperfusions, as reflected by steady deterioration of PCO_2 and pH after each reperfusion.

The in-line and in-situ measurement of blood gases resulted to be a not trivial task. Indeed in several cases not all the data could be recorded, with a more frequent fault of PCO_2 and PO_2 probes. However our findings, in agreement with Khuri and coworkers [8, 15], seems to indicate pH measurement as an effective and reliable index of myocardial tissue distress during open heart cardiac surgery.

V. Conclusions

Although the final clinical significance of the observed patterns needs validation on larger population and correlation with adverse postoperative outcomes, our study indicates that for prolonged cross clamping time intermittent warm cardioplegia may be inadequate in reversing ischemia, and an 'ischemic debt' may build up at every ischemia/reperfusion. Progressive increase of reperfusion durations or direct monitoring of myocardial oxygenation could be advisable in case of prolonged cross-clamping time.

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