Metabolic monitoring during continuous warm- and cold-blood cardioplegia by means of myocardial tissue pH and PO_2

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Objectives: To study the changes in myocardial tissue pH and PO_2 during cold- and warm-blood cardioplegic arrests.

Design: An experimental study in dogs.

Methods: Nine dogs underwent the following procedures: 30 minutes with an empty heart beating under cardiopulmonary bypass (control period); 30 minutes of warm (33 °C) cardioplegic arrest with a 1:4 mix of crystalloid in blood solution administered continuously at 150 mL/min; 30 minutes of cold (15 °C) cardioplegic arrest; and 30 minutes of myocardial reperfusion. The cardioplegic blood solution was administered antegradely through the ascending aorta.

Main outcome measures: Tissue pH and PO_2. Arterial and coronary sinus oxygen content and myocardial consumption calculated.

Results: There was a modest but significant increase in the left anterior descending (LAD) and circumflex (Cx) tissue pH throughout the experiment. PmO_2 in the LAD territory averaged 44 (7) mm Hg (mean and standard error of the mean) during the bypass period, 123 (23) mm Hg at the termination of warm cardioplegic arrest, 146 (28) mm Hg at the end of cold arrest and 66 (17) mm Hg after reperfusion. Oxygen consumption averaged 0.65 (0.15) mL/min during the bypass period, 0.3 (0.18) mL/min at the end of warm arrest, 0.25 (0.16) mL/min at the end of cold arrest and 0.45 (0.08) mL/min after reperfusion ($p < 0.05$). Oxygen delivery to the LAD territory was greater than myocardial oxygen consumption by an average of 2.02 (0.4) mL/min during bypass, 2.02 (0.62) mL/min after warm arrest, 2.12 (0.5) mL/min after cold arrest and 1.55 (0.25) mL/min after reperfusion ($p > 0.05$).

Conclusions: During cardioplegic arrest, tissue PO_2 increased and oxygen consumption decreased significantly, whereas tissue pH remained normal, suggesting that continuous warm- and cold-blood cardioplegia maintained aerobic glycolysis during myocardial arrest. Thus, the increase in myocardial tissue PmO_2 during cardioplegic arrest reflects the decrease in myocardial oxygen consumption while maintaining oxygen supply.

Objectifs : Étudier les changements du pH et de la PO_2 du tissu du myocarde pendant un arrêt cardioplégique à sang froid et à sang chaud.

Conception : Étude expérimentale sur des chiens.

Méthodes : Neuf chiens ont subi les interventions suivantes : 30 minutes avec cœur vide battant en circulation extracorporelle (période témoin); 30 minutes d'arrêt cardioplégique à chaud (33 °C) avec un mélange 1:4 de cristalloïde en solution sanguine administré sans interruption à raison de 150 mL/min; 30 minutes d'arrêt cardioplégique à froid (15 °C); et 30 minutes de reperfusion du myocarde. La solution de sang cardioplégique a été administrée de façon antérograde par l'aorte ascendante.

Principales mesures de résultats : pH et PO_2 tissulaires. Contenu en oxygène des artères et du sinus coronaire et consommation du myocarde calculés.

Résultats : On a constaté une augmentation modeste mais significative du pH du tissu de l'artère interventriculaire antérieure (AIA) et de l'artère circonflexe (Cx) pendant toute l'expérience. La

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P_{MO_2} dans la région de l'AIA s'est établie en moyenne à 44 (7) mm de Hg (médiane et erreur type ou moyenne) au cours de la période de circulation extracorporelle, 123 (23) mm de Hg à la fin de l'arrêt cardioplégique à chaud, 146 (28) mm de Hg à la fin de l'arrêt à froid et 66 (17) mm de Hg après la reperfusion. La consommation d'oxygène s'est établie en moyenne à 0,65 (0,15) mL/min. au cours de la période de circulation d'extracorporelle, 0,3 (0,18) mL/min à la fin de l'arrêt à chaud, 0,25 (0,16) mL/min. à la fin de l'arrêt à froid et 0,45 (0,08) mL/min. après la reperfusion ($p < 0,05$). L'apport d'oxygène dans la région de l'AIA a dépassé la consommation d'oxygène dans le myocarde en moyenne de 2,02 (0,4) mL/min. au cours de la période de circulation extracorporelle, de 2,02 (0,62) mL/min. après l'arrêt à chaud, de 2,12 (0,5) mL/min. après l'arrêt à froid et de 1,55 (0,25) mL/min. après la reperfusion ($p > 0,05$).

CONCLUSIONS : Au cours de l'arrêt cardioplégique, la P_{O_2} tissulaire a augmenté et la consommation d'oxygène a diminué considérablement, tandis que le pH tissulaire est demeuré normal, ce qui indique que la cardioplégie continue à sang chaud et à sang froid a maintenu la glycolyse aérobie au cours de l'arrêt du myocarde. L'augmentation de la P_{MO_2} du tissu du myocarde au cours de l'arrêt cardioplégique démontre donc que la consommation d'oxygène du myocarde a diminué pendant que l'apport se maintenait.

Although blood cardioplegic arrest of the heart has become the optimal technique for preventing ischemic injury during cardiac surgery, the temperature at which to administer cardioplegic solutions remains controversial. Both cold- and warm-blood arrests have been used successfully in clinical practice. Myocardial oxygen consumption, lactate release and acid washout are higher in warm- than in cold-protected hearts.[1] Moreover, since there is no simple, effective method for assessing the metabolic status of the myocardium during surgery, the adequacy of both cardioplegic distribution and myocardial protection with the warm technique remains of concern.

The objective of this study was to compare the effects of continuous warm- and cold-blood cardioplegic arrest on myocardial oxygen levels and acid metabolism as measured by interstitial myocardial oxygen pressure (P_{O_2}) and pH probes. The hypotheses we tested were that oxygen delivery exceeds myocardial needs during cardiopulmonary bypass (CPB) with both warm- and cold-blood cardioplegic infusions, and that online monitoring of myocardial tissue pH and P_{O_2} could be useful for assessing acid and oxygen metabolism during cardioplegic arrest.

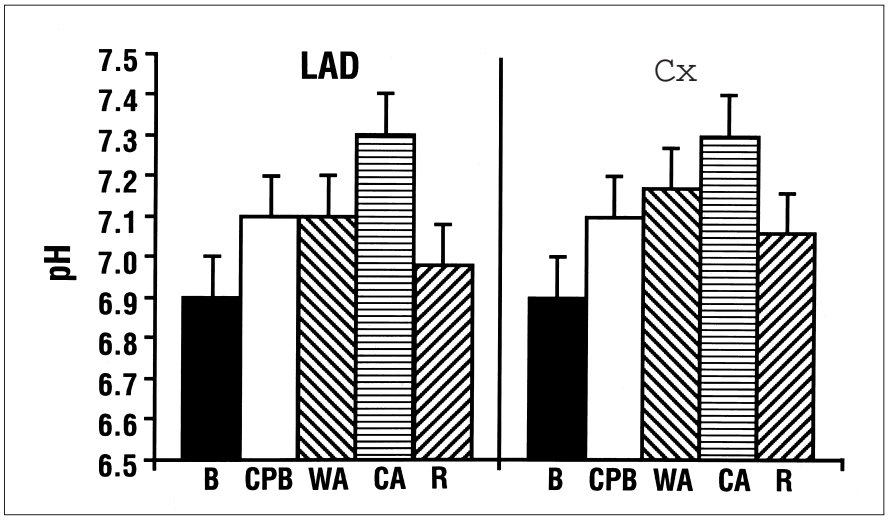

FIG. 1. Changes in interstitial tissue pH in the left anterior descending (LAD) and the circumflex (Cx) coronary artery territories, measured before the start of cardiopulmonary bypass (CPB) (baseline [B]), after 30 minutes of CPB, after 30 minutes of warm cardioplegic arrest (WA), after 30 minutes of cold arrest (CA) and after 30 minutes of reperfusion (R). Tissue pH increased significantly ($p = 0.01$) during warm and cold cardioplegic arrest.

METHOD

Nine dogs, ranging in weight between 25 and 30 kg, were anesthetized with sodium pentobarbital (30 mg/kg) and ventilated with a Harvard respirator (Harvard Apparatus, South Natick, Mass.). After median sternotomy and systemic heparinization (3 mg/kg), the left femoral artery was cannulated for arterial inflow and the right atrium for venous return, and the cannula was connected to a bubble oxygenator (Baxter Healthcare, Irvine, Calif.). The coronary sinus was cannulated through a transatrial approach for blood sampling, and the left ventricle was vented through a line in the apex. A cannula for cardioplegia delivery and arterial blood sampling was placed and secured in the ascending aorta.

The systemic temperature was maintained at 37 °C throughout the CPB. The cardioplegic solution was composed of oxygenated blood diluted 4:1 with a crystalloid solution containing 130 mmol of sodium, 135 mmol of chloride, 3 mmol of calcium, 28 mmol of lactate, 20 g of mannitol, 0.17 g of sodium bicarbonate, and either 80 mmol (high concentration) or 34 mmol (low concentration) of potassium chloride (KCl)/L. The pH of the crystalloid solution was 7.4 and the osmolarity 360 mOsm/L. The cardioplegic solution was administered antegradely through the infu-

sion cannula in the ascending aorta.

After CPB was instituted, all animals were subjected to 30 minutes of empty beating heart. Then, warm cardioplegic arrest was obtained with an infusion of 200 mL of blood-based cardioplegic solution at high KCl concentration followed by a continuous infusion (150 mL/min) of the low KCl concentration solution for 30 minutes. Cold arrest was achieved by decreasing the temperature of the cardioplegic solution to 15 °C for 30 minutes. Finally, at the end of the experiment, myocardial reperfusion was performed for 30 minutes. Blood sampling for oxygen and metabolic monitoring was performed before initiating CPB (baseline), after 30 minutes of empty beating heart on CPB, after the 30-minute periods of warm arrest and cold arrest and after the 30 minutes of reperfusion.

Intramyocardial pH

Throughout the experiment, interstitial myocardial pH was measured with a pH probe (Vascular Technology, North Chelmsford, Mass.). A reference electrode was placed in the mouth of the animal in contact with the saliva. Both electrodes were connected to an electronic pH-meter unit and a computer acquisition board. Data acquisition, processing, analysing and monitoring were performed by the computer. A thermoneedle probe was used to monitor myocardial temperature and to calculate the temperature-corrected interstitial myocardial pH on the basis of the Nernst equation. Both the pH and the thermoneedle electrodes were positioned in the anterior wall in the left anterior descending (LAD) artery territory and in the lateral wall in the circumflex (Cx) artery territory of the left ventricle. The pH electrodes were calibrated before each experiment using a standard laboratory buffer solution with a pH of 7 at 35 °C. Tissue myocardial pH was recorded every 2 seconds during the experiment, and the averages were calculated for standardized periods of 100 seconds throughout the experiment.

Intramyocardial Po_2

A smooth, flexible polyethylene microcatheter (polarographic Clark type, 470-µm diameter, 5-mm long sensitive area; GMS, Germany) was inserted in the anterior wall to measure interstitial Po_2 in the midmyocardium. Precalibration values from the manufacturer were used (probe's zero current < 2 nA, temperature sensitivity of 4.5%/°C) and the probe's sensitivity was determined in ambient air using a polarographic potential of 795 mV. At this potential and at 35 °C, the catheter response time is 70 seconds and the sensitivity is 2.5 nA/mm Hg Po_2. The typical sensitivity drift is ± 10%/10 d and the typical zero drift is ± 2 nA/10 d. The ambient air Po_2 was previously determined by measuring the barometric pressure (mm Hg), the ambient temperature (°C) and the relative humidity (%). Assuming a 20.95% oxygen ambient air content, we calculated the ambient Po_2 according to the following formula:

Po_2 = (barometric pressure – water vapour pressure) × 20.95% oxygen, which was then associated to the sensitivity current. The calibration was linear from 0% to 20.95% oxygen, with an expected sensitivity calibration error of less than ± 1% of the true Po_2 value and a zero calibration error of less than 1 mm Hg Po_2. The current from the oxygen pressure (Pmo_2) catheter was recorded continuously and converted "online" to Po_2 data, with direct temperature correction. The temperature was measured using the small thermistor inserted in the myocardium adjacent to the Po_2 catheter and pH probe.

Myocardial oxygen metabolism

Throughout the experiments, blood flow in the LAD and the circumflex (Cx) coronary arteries was measured using ultrasonic flow probes. Arterial

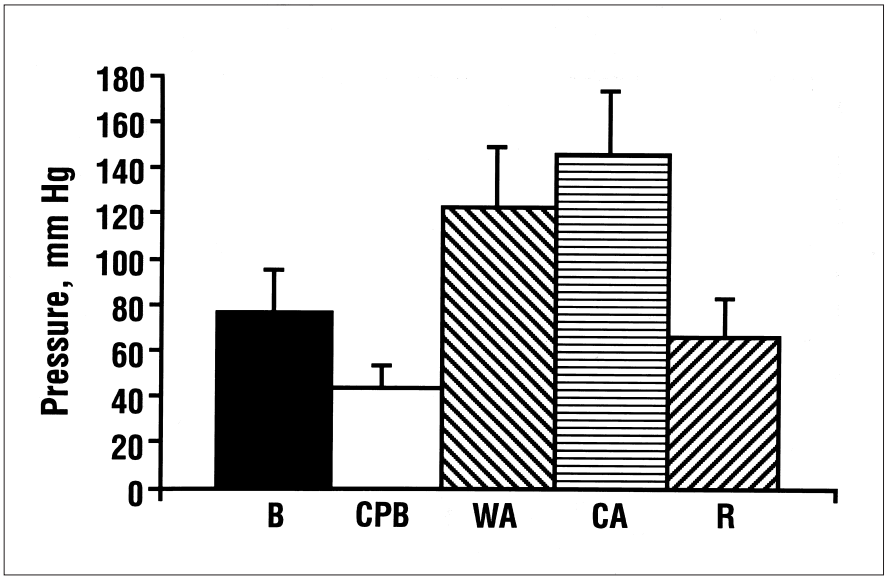

FIG. 2. Changes in interstitial tissue oxygen partial pressure Po_2 (mm Hg) in the left anterior ventricle. Tissue Po_2 increased significantly ($p = 0.001$) during warm arrest (WA) and cold arrest (CA). B = baseline, CPB = cardiopulmonary bypass, R = reperfusion.

and coronary sinus blood samples were harvested to measure the hematocrit (%), oxygen saturation (%) and lactate concentration (mmol/L). Blood oxygen content was calculated as follows: hemoglobin level × percent oxygen saturation × hemoglobin binding coefficient (1.34). Myocardial oxygen delivery to the left anterior and the circumflex bed (in mL/min) was determined as follows: aortic blood oxygen content × LAD or Cx coronary blood flow (CBF).[2] Myocardial oxygen consumption in the bed of the LAD and the Cx (in mL/min) was calculated as follows: (aortic oxygen content – coronary sinus oxygen content) × CBF of the LAD or Cx coronary artery. Myocardial oxygen excess (in mL/min) was estimated by subtracting oxygen consumption from oxygen delivery. Myocardial lactate release was calculated by subtracting arterial serum lactate concentration from blood content in the coronary sinus.

Data analysis

The data are presented as means (plus or minus standard error). Differences between the various periods of the experiments were analysed by repeated measures analysis of variance for a 2-factor design (Solo; BMDP Statistical Software, Los Angeles, Calif.). We tested the hypotheses that there were differences in myocardial tissue pH, P_{O_2}, myocardial oxygen metabolism and lactate release during the 5 periods of each experiment (baseline, CPB, warm-blood arrest, cold-blood arrest and reperfusion). The level of statistical significance was established at 95% with a p value of < 0.05. All animals received human care in compliance with the *Guide for the Care and Use of Laboratory Animals*.[3]

Results

Myocardial tissue pH and P_{O_2}

There was a significant increase in tissue pH: from 6.9 (0.1) before the CPB to 7.1 (0.1) after warm cardioplegic arrest at 33 °C and to 7.3 (0.1) after the period of cold cardioplegic infusion in the LAD and Cx coronary territories at 15 °C ($p = 0.01$) (Fig. 1). Tissue P_{O_2} increased from 44 (7) mm Hg after 30 minutes of empty beating heart during total CPB to 123 (23) mm Hg during warm cardioplegic arrest, and to 146 (28) mm Hg during cold cardioplegic infusion. These dif-

Table I

Measurements of Myocardial Oxygen, Delivery, Consumption and Excess During the 5 Periods (Baseline, Empty Beating Heart, Warm Cardioplegic Arrest, Cold Cardioplegic Arrest and Reperfusion)*

Measurement	Baseline	Empty beating heart	Warm arrest	Cold arrest	Reperfusion	p value
Arterial pH	7.45 (0.03)	7.36 (0.04)	7.30 (0.04)	7.25 (0.04)	7.20 (0.04)	0.003
Venous pH	7.45 (0.03)	7.37 (0.03)	7.30 (0.03)	7.27 (0.04)	7.23 (0.04)	0.007
Arterial P_{O_2}, mm Hg	333 (51)	276 (40)	253 (38)	268 (25)	263 (40)	0.12
Arterial oxygen saturation, %	99 (1)	99 (1)	99 (1)	100	96 (3)	0.45
Venous P_{O_2}, mm Hg	32 (3)	46 (4)	105 (20)	249 (26)	72 (14)	0.0001
Venous oxygen saturation, %	58 (7)	74 (5)	91 (3)	98 (1)	82 (4)	0.0001
LAD oxygen delivery, mL/min	3.29 (0.8)	2.67 (0.51)	2.32 (0.79)	2.36 (0.65)	2.0 (0.29)	0.24
LAD MVO_2, mL/min	1.64 (0.6)	0.65 (0.15)	0.3 (0.18)	0.25 (0.16)	0.45 (0.08)	0.003
LAD oxygen excess, mL/min	1.65 (0.31)	2.02 (0.4)	2.02 (0.62)	2.12 (0.5)	1.55 (0.25)	0.54
Cx oxygen delivery, mL/min	6.54 (1.18)	5.6 (0.93)	3.72 (0.64)	3.59 (0.72)	4.49 (0.9)	0.02
Cx MVO_2, mL/min	2.76 (0.68)	1.38 (0.38)	0.33 (0.13)	0.21 (0.12)	1.03 (0.29)	0.0001
Cx oxygen excess, mL/min	3.79 (0.89)	4.21 (0.66)	3.39 (0.61)	3.38 (0.7)	3.46 (0.73)	0.77

*Figures are given as mean (and standard error of the mean). Venous = coronary sinus, LAD = left anterior descending coronary artery, Cx = circumflex coronary artery, MVO_2 = myocardial oxygen consumption

ferences in tissue PO_2 were highly significant ($p = 0.001$) (Fig. 2).

Myocardial oxygen metabolism

Averaged arterial blood PO_2 varied from 253 to 333 mm Hg during the experiment (Table I). Venous PO_2 in the coronary sinus increased from 32 (3) mm Hg at baseline to 249 (26) mm Hg during cold cardioplegic injection ($p = 0.001$), and oxygen saturation increased from 58 (7)% at baseline to 98 (1)% during cold cardioplegia ($p = 0.001$) (Table I).

Oxygen delivery in the anterior wall of the left anterior ventricle remained stable throughout the experiment, whereas oxygen consumption decreased from 1.64 (0.6) mL/min to 0.3 (0.18) mL/min after warm cardioplegic arrest and to 0.25 (0.16) mL/min after cold cardioplegic arrest ($p = 0.003$). The excess myocardial oxygen (delivery – consumption) did not increase significantly during cardioplegic injection ($p = 0.54$) (Table I). Oxygen consumption in the Cx territory decreased from 2.76 (0.68) mL/min at baseline to 0.33 (0.13) mL/min during warm cardioplegia and to 0.21 (0.12) mL/min during cold cardioplegia ($p = 0.0001$) (Table I). Although oxygen delivery decreased significantly ($p = 0.02$) from 6.54 (1.18) mL/min at baseline to 3.59 (0.72) mL/min during cold cardioplegic infusion, there was no significant change ($p = 0.77$) in the excess of oxygen delivered to the myocardium irrigated by the circumflex coronary artery (Table I).

Myocardial lactate release

There was no release of myocardial lactate throughout the various periods of CPB, warm and cold cardioplegic injections and myocardial reperfusion. Moreover, the differences in arterial and coronary sinus lactate were slightly negative (Fig. 3).

Discussion

Cold and warm cardioplegic arrest

Cold- and warm-blood cardioplegic solutions are currently being used in clinical practice to prevent ischemic injury during cardiac surgery. Both approaches have strong advocates and opponents. Hayashida and associates[1] showed that antegrade warm-blood cardioplegia resulted in greater myocardial oxygen consumption and lactate and acid release than cold injection of the cardioplegic blood solution, although the administration of the solution was intermittent to improve visualization during each distal coronary anastomosis. These data showed that intermittent blood cardioplegia did not support the aerobic metabolism. Although left ventricular function was better preserved in a warm- than in cold-protected heart in the last study,[1] Bufkin and associates[4] have suggested that cold-blood cardioplegia results in better protection of myocardial function.

Several studies have shown that the use of blood as the vehicle for cardioplegic solutions creates conditions of aerobic glycolysis during cardioplegic arrest.[5] Engelman and associates[5] showed that oxygen consumption averaged 2.6 (0.38) mL/min during cold-blood cardioplegic administration and that oxygen delivery largely exceeded myocardial consumption, although lactate was produced by the myocardium, suggesting that anaerobic glycolysis was also present. Buckberg and associates[6] found that myocardial oxygen consumption decreased from 5.59 (1.95) mL/100 g/min^{-1} to 1.1 (0.41) mL/100 g/min^{-1} in the arrested heart at 37 °C and to 0.31 (0.12) mL/100 g/min^{-1} in hearts maintained at 22 °C.

Although oxygen delivery to both LAD and Cx myocardial territories decreased from baseline with empty beat-

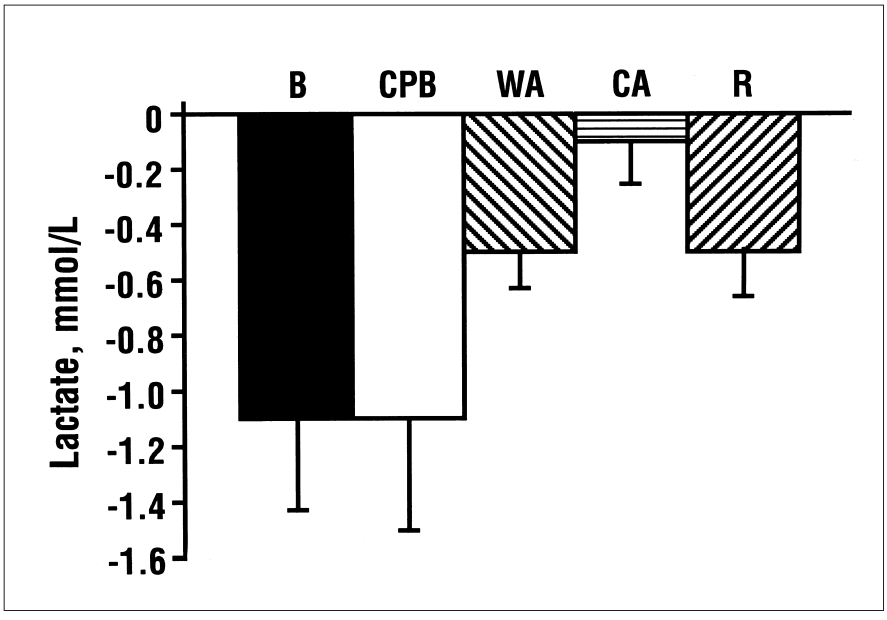

FIG. 3. Myocardial lactate release during cardioplegic arrest. There was no release of lactate from the myocardium during warm arrest (WA) and cold arrest (CA) , although the difference between the 5 periods of the experiment was significant ($p = 0.001$). B = baseline, CPB = cardiopulmonary bypass, R = reperfusion.

ing hearts and warm and cold arrested hearts, oxygen was always delivered in excess of consumption (Table I). Moreover, oxygen consumption in the LAD territory decreased by 82% during warm cardioplegic arrest and 85% during cold cardioplegic arrest, and in the Cx area by 88% during warm cardioplegic arrest and 92% during cold cardioplegic arrest. There was no myocardial production of lactate, and tissue pH increased, suggesting that aerobic glycolysis was maintained during periods of warm and cold arrest. Therefore, the present study confirms that aerobic metabolism of the myocardium can be maintained with continuous delivery of either cold- or warm-blood cardioplegia and that the effect of the administered solution's temperature on myocardial oxygen metabolism was similar, with cold protection resulting in a slightly lower myocardial oxygen consumption than warm protection, although oxygen delivery far exceeded the needs in all hearts.

Myocardial tissue pH and P_{O_2}

In this study, the P_{mO_2} increased significantly during warm and cold cardioplegic arrest (Fig. 2); similar changes were also shown in oxygen pressure and saturation from venous sampling in the coronary sinus (Table I). Several studies have suggested that myocardial tissue P_{mO_2} reflects the difference between oxygen delivery and consumption.[7–9] Nollert and colleages[9] showed that myocardial tissue P_{mO_2} in the right ventricle decreased to minimum values of 2 mm Hg during ischemia, and Wiener and colleagues[8] reported that subendocardial P_{mO_2} averaged 11 (1.5) mm Hg under normal conditions in the dog. Myocardial oxygen pressure averaged 44 (7) mm Hg in beating empty hearts and increased to 123 (23) mm Hg in warm arrested hearts and to 146 (28) mm Hg in cold arrested hearts (Fig. 2). Thus, the increase in myocardial tissue P_{mO_2} during warm and cold cardioplegic arrest reflects a significant decrease in oxygen consumption while delivery of oxygen was maintained. Moreover, there was no sign of anaerobic glycolysis, suggesting that aerobic metabolism was sustained during cardioplegia, reflected by high values of P_{mO_2}.

The data presented suggest that online monitoring of myocardial tissue pH and P_{O_2} could become a valuable tool for evaluating the level of protection from ischemic injury obtained with the current clinical blood cardioplegic approach. It has been suggested that periods of warm ischemic arrest with cardioplegia longer than 10 minutes and periods of cold ischemic arrest longer than 20 minutes cause detrimental metabolic and ischemic changes in the myocardium.[10] Although anaerobic threshold[11] with myocardial P_{O_2} and lactate release was not determined in the present study, we have shown that continuous warm- and cold-blood cardioplegic administration effectively maintained aerobic metabolism of the myocardium in the normal dog, and that an increase in P_{mO_2} reflects a decrease in myocardial oxygen consumption. It remains to be shown that aerobic metabolism can be sustained with changes in flow rate, temperature and site of administration of the cardioplegic solution during intermittent use of cardioplegia, and that online monitoring of tissue pH and P_{mO_2} can be used to monitor metabolic changes stemming from intermittent myocardial ischemia.

Limitations of the study

The measurement of interstitial pH and P_{O_2} with solid probes was limited to the midmyocardium because of the physical forms of both probes. Thus, hypoxia and acidosis occurring in the endocardium could have been missed by our method. Also, placing the probes in a beating heart may cause local tissue injury and may have an effect on the local measurement of these 2 markers of tissue viability. Also, we need more information on changes in interstitial myocardial P_{O_2} during periods of ischemic arrest to further assess the potential clinical value of the measurements.

Conclusions

Continuous warm (33 °C) and cold (15 °C) blood cardioplegia maintained aerobic glycolysis during myocardial arrest. Both temperatures of the cardioplegic solution have a similar effect on myocardial oxygen metabolism. The increase in myocardial tissue P_{mO_2} during cardioplegic arrest reflects the decrease in myocardial oxygen consumption while maintaining oxygen supply. We believe that online monitoring of myocardial tissue pH and P_{O_2} during blood cardioplegic arrest may be valuable tools to evaluate myocardial protection from ischemia and to help maintain aerobic glycolysis during cardiac surgery. Additional experiments to define anaerobic threshold and to simplify the method of pH and P_{mO_2} monitoring are needed to assess the possibility of clinical use.

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