Experimental Studies

Is Coronary Sinus Blood Oxygen Tension Behavior Determined by Myocardial Oxygen Tension Variation during Cardiac Reperfusion?

Antonio Carlos CICOGNA, M.D., Paulo José Ferreira TUCCI, M.D., Joel SPADARO, M.D., Maria Aparecida Marchesan RODRIGUES, M.D., Paulo Roberto CURI, M.D., *and* Pedro Hélio LUCCHIARI

SUMMARY

The relationship between coronary sinus blood oxygen tension ($CSPO_2$) and myocardial oxygen tension (MPO_2) variations during cardiac ischemia and reperfusion was studied in anesthetized open-chest dogs. Oxygen tension was measured by a polarographic method. Ischemia resulted in a slightly decreased $CSPO_2$ and a more pronounced reduction of MPO_2. After reperfusion the $CSPO_2$ rose rapidly and transiently before it returned gradually to the control level. By contrast, during the recovery period, the MPO_2 increased slowly, with recovery occurring long after the peak of $CSPO_2$. These data suggest that during the reperfusion phase, the $CSPO_2$ variation is probably due to opening of the myocardial arteriovenous shunts instead of an increase of flow through the myocardial capillary bed.

Additional Indexing Words:

Myocardial oxygen tension — Coronary sinus blood oxygen tension — Polarography — Cardiac ischemia — Reperfusion

PREVIOUS studies[1)-4)] have revealed that coronary sinus blood oxygen tension ($CSPO_2$) increases rapidly and phasically after coronary occlusion or anoxic cardiac arrest. The mechanism involved in this $CSPO_2$ response is not well established. The high oxygen saturation of the coronary venous blood is believed to be the result of an increased flow through the capillary bed, causing a decrease in the myocardial oxygen extraction or arteriovenous shunting.[1),3),5),6)] The first hypothesis was based on authors who verified that reactive hypermia is always associated with an elevation of myocardial oxygen tension (MPO_2) values above those observed before coronary occlusion. However, changes in $CSPO_2$ and MPO_2 were not recorded simul-

From the Departments of Medicine, Pathology and Biophysics, Medical School of Botucatu, State University "Julio de Mesquita Filho", Botucatu, State of São Paulo, Brazil.

Address for reprint: Dr. Antonio Carlos Cicogna, Departamento de Clinica Medica, Faculdade de Medicina de Botucatu, Botucatu, São Paulo, Brasil 18610.

Received for publication December 3, 1986.

Manuscript revised June 22, 1987.

taneously and continuously. Simultaneous measurements are needed to test the hypothesis that a quick and transient elevation of $CSPO_2$ is dependent on MPO_2 variations. This study was undertaken to determine if the changes in oxygen tension of the coronary sinus effuent after coronary occlusion are determined by changes in intramyocardial oxygen tension. The $CSPO_2$ and MPO_2 were recorded simultaneously by a polarographic method during cardiac ischemia and reperfusion.

Methods

Studies were performed in 7 male adult mongrel dogs, weighing from 15 to 20 kg. They were anesthetized with sodium pentobarbital (20 mg/kg/iv) and morphine (2 mg/kg/im); additional anesthetic was administered as required. After endotracheal intubation, respiration was maintained with a mechanical respirator and supplementary oxygen was administered to keep the arterial pH, oxygen and carbon dioxide tensions within the physiological range. The thorax was opened and the heart suspended in a pericardial cradle so that the anterior aspect of the left ventricle was exposed. The initial portion of the left anterior descending artery was dissected free so that it could be occluded when desired and the probe of an electromagnetic flowmeter (Biotronex BL610) was applied. A zero-flow reference were obtained by occluding the vessel distal to the probe. The calibration was done with isolated arteries of suitable length and diameter, which were cannulated at both ends and perfused with blood from a gravity feed reservoir into a graduated cylinder. Aortic pressure was measured by means of a catheter placed in the thoracic aorta.

The myocardial oxygen tension was measured in the endocardial layers of the left ventricle perfused by left anterior descending artery (LAD) with a cyanomethacrylate glue insulated platinum electrode (183 μ diameter). The tip of the electrode was freed from insulation for 1 mm. In order to fix the electrode in the surface of dry myocardium, a thin layer of a cyanomethacrylate glue was applied to its base, just before its implantation in the muscle. The electrodes were also sutured in the myocardium.

For the measurement of coronary sinus blood oxygen, a glass insulated platinum electrode (0.1–0.2 mm free of insulation) with 1 mm of diameter was positioned in a silastic tube. This catheter was inserted at least 2–3 cm into the coronary sinus via the right atrium. The entire volume of coronary sinus blood flow was withdrawn at a rate of 12 ml/min, and returned to the dog via the right external jugular vein. Koberstein et al[7] have demonstrated that the sinus coronary blood may be withdrawn at this rate without atrial

contamination.

The electrodes used to measure oxygen tension were polarized at −0.6 V and the circuit was completed using a reference calomel half-cell electrode with a saline bridge connected directly to the subcutaneous tissue of the animal. The polarographic current flow resulting from the diffusion of oxygen to the platinum electrodes was measured by a current amplifier* with a time constant of 1.1 sec.[8] Since the polarographic current is directly proportional to the concentration of oxygen,[9)-12)] the relative current variation allows one to infer the relative PO_2 variations.

The " in vitro " response of each single electrode was determined for different concentrations of oxygen in saline solution at room temperature. To verify if the electrodes were responding properly after myocardial fixation, LAD occlusion was performed before each experiment. Simultaneous recordings of MPO_2 and $CSPO_2$ were made before (t_0 time), after 60 sec of myocardial ischemia (t_1 time) and after release of coronary occlusion. In the post anoxia period the variables were measured at the peak oxygen saturation of coronary sinus blood (t_2 time). The arterial pressure, mean coronary blood flow and oxygen tension were also recorded on a multichannel recorder (DR8—Electronic for Medicine).

At the completion of the study, the dogs were sacrificed, the hearts examined and the positions of the coronary sinus catheter and the depth of the tissue electrode were verified. Blocks of myocardial tissue surrounding each electrode were removed and submitted for histologic study.

Values are expressed as mean±SEM. Statistical differences between the three parameters were evaluated by the analysis of variance for repeated measures and between two parameters by paired Student's t-test.

Results

Histological studies: The histological examination of the myocardium showed minimal compression, degeneration and necrosis of the muscle fibers near the electrode tip. Hematomas, fibrin or leukocyte exudates were not observed.

Oxygen tension and hemodynamic changes: A typical response to coronary occlusion is shown in Fig. 1. Simultaneous $CSPO_2$ and MPO_2 measurement during myocardial ischemia showed a slight decrease of $CSPO_2$ and a more pronounced MPO_2 decrease. After coronary reperfusion $CSPO_2$ rose transiently above baseline values; thereafter, there was a gradual return

* Polarograph was made by Prof. P. H. Lucchiari, from the Department of Biophysics, State University " Julio de Mesquita Filho ", State of São Paulo, Brazil.

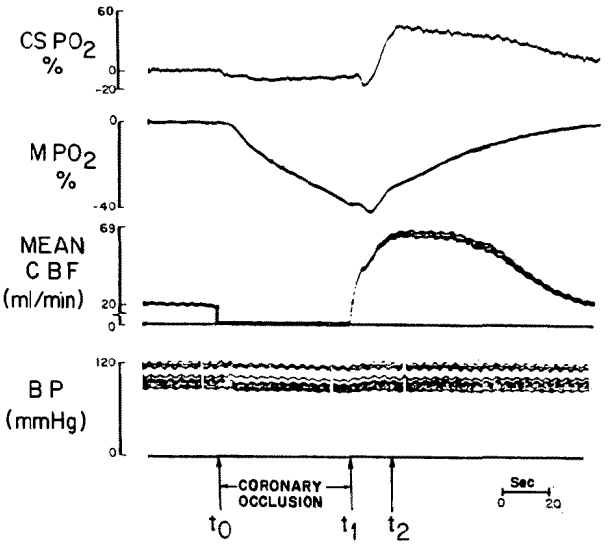

Fig. 1. Effect of coronary occlusion on coronary sinus blood oxygen tension ($CSPO_2$), myocardial oxygen tension (MPO_2), mean coronary blood flow (CBF) and blood pressure (BP).

Table I. Effects of Coronary Occlusion on Cardiac Variables

	SAP/DAP			CBF			MPO_2		$CSPO_2$	
	t_0	t_1	t_2	t_0	t_1	t_2	Δ_1	Δ_2	Δ_1	Δ_2
	mmHg			ml/min			%		%	
	116/94	108/88	118/94	23	0	99	−26.2	+5.0	−9.0	+36.0
	108/86	108/86	106/82	14	0	102	−59.0	+59.0	0.0	+20.0
	86/64	86/64	87/61	26	0	78	−96.2	−24.5	−4.8	+38.0
	110/77	97/69	108/77	32	0	58	−38.2	−14.3	−8.0	+36.3
	112/85	106/73	112/82	16	0	52	−71.2	−10.2	0.0	+50.0
	112/91	88/54	105/79	22	0	55	−95.0	−75.0	0.0	+22.2
	118/83	114/77	118/80	20	0	69	−43.4	−31.5	−10.3	+55.1
	98*	95*	98*	29	0	78	−23.5	−23.5	−7.9	+30.0
$\bar{X}$	109/83	101/73	108/79	23	—	77	−56.5	−14.3	−5.0	+35.9
SEM	3.5/3.2	3.5/3.9	3.4/3.2	2.1	—	7.7	10.1	13.3	1.5	4.3

SAP = systolic aortic pressure; DAP = diastolic aortic pressure; MPO_2 = myocardial oxygen tension; $CSPO_2$ = coronary sinus blood oxygen tension; CBF = mean coronary blood flow. t_0: recording time of variables before coronary occlusion; t_1: recording time of variables during coronary occlusion; t_2: recording time of variables after coronary occlusion in the peak oxygen saturation of coronary sinus blood; Δ_1: variation between t_0 and t_1; Δ_2: variation between t_2 and t_0; mmHg: millimeter of mercury; %: percent of variation; ml/min: millimeter by minute; $\bar{X}$: mean of values; SEM: standard error mean. * mean arterial pressure (this value was not used for calculation of the $\bar{X}$ and SEM of SAP and DAP).

to control level. In contrast, the MPO_2 presented a slow elevation, and a full recovery occurred far from the peak of $CSPO_2$.

Table I depicts the changes in MPO_2, mean coronary blood flow (CBF) and blood pressure behavior in the experiment. At the release of occlusion (t_1), there was a significant decrease in systolic arterial pressure ($p<0.05$). A consistent finding was a substantial decrease in MPO_2 ($-56.5\pm10.1\%$), while $CSPO_2$ suffered only a slight reduction ($-5.0\pm1.5\%$). After coronary reperfusion (t_2) the CBF increased to $263.9\pm58.2\%$ (23 ± 2.1 to 77 ± 7.7 ml/min; $p<0.001$) of the control level. The MPO_2 values remained below the basal state (-14.3 ± 13.3). The corresponding values of $CSPO_2$ were substantially larger that the control level ($+35.9\pm4.3\%$). In all except one experiment, the MPO_2 was smaller than $CSPO_2$ t_2 time.

Discussion

Since the pioneering work of Davies and Brink,[13] the implanting of microelectrodes in animal tissues has been used for the measurement of oxygen tension.[8),14)-24)] The interpretation of oxygen tension measured by the bare-tipped platinum electrode technique requires an accurate estimation of the possible errors. The potential problems associated with the polarographic method have been well described:

1. the cathode current is dependent on the diffusion constant of oxygen in tissue;
2. the negatively polarized electrode itself consumes oxygen;
3. denaturation of protein on the electrode;
4. movement of either the electrode tip or the fluid around the tip;
5. damage to local tissue by electrode dimensions. All these shortcomings have been discussed in previous reports.[9),18),19),22),23),25)-28)] Errors like 1 and 2 mentioned above are inherent in every polarographic measurement; the other errors are dependent upon needle electrodes. Taking into account that in the present investigation the tissue damage was minimal, the electrode appeared to be well fixed in the myocardial surface, the flow rates around the electrode tip positioned into the coronary sinus catheter was constant and the time between two successive records was short, we believe that the oxygen tension measurement reflects PO_2 conditions.

Coronary artery occlusion promoted an important decrease in the subendocardial oxygen tension and a slight decrease in the $CSPO_2$. The MPO_2 behavior is in agreement with other studies.[15)-17),21),22),29),30)]

Similar to previous studies,[1)-3)] we have observed in all the dogs, im-

mediately after coronary reperfusion, that $CSPO_2$ rose in a quick and transitory fashion above its control level. On the other hand, the MPO_2 showed a slow ascending slope during reactive hyperemia. In only one dog, a rapid and important enhancement of MPO_2 was observed. The MPO_2 behavior is quite similar to data reported by Sayen et al, 1958[16] and Winbury et al, 1971.[21] These authors have emphasized that the overshoot of myocardial oxygen tension was not consistent in the post anoxia period; in the great majority of experiments a gradual increase of MPO_2 occurred.

The MPO_2 behavior which was observed in the present investigation raises the hypothesis that the high oxygen saturation of the coronary venous blood probably is due to the opening of myocardial arteriovenous shunts instead of an increase of flow through the myocardial capillary bed. In one dog, the rapid and transitory rise of MPO_2, resulting in a decrease in the myocardial oxygen extraction due to an increase in coronary flow, could explain the quick and transitory elevation of $CSPO_2$. However, the slow MPO_2 variation in all the other dogs is not in accordance with the fast $CSPO_2$ changing during reactive hyperemia. In conclusion, this study suggests that the increase in the $CSPO_2$ values post cardiac ischemia could be related to the opening of arteriovenous shunts.

References

1. Coffman JD, Gregg DE: Oxygen metabolism and oxygen debt repayment after myocardial ischemia. Am J Physiol **201**: 881, 1961
2. Olsson RA, Gregg DE: Metabolic responses during myocardial reactive hyperemia in the unanesthetized dog. Am J Physiol **208**: 231, 1965
3. Brantigan JW, Perna AM, Gardner TJ, Gott VL: Intramyocardial gas tensions in the canine heart during anoxic cardiac arrest. Surg Gynec Obstet **134**: 67, 1972
4. Ruiter JH, Spaan JAE, Laird JD: Transient oxygen uptake during myocardial reactive hyperemia in the dog. Am J Physiol **235**: H87, 1978
5. McGregor M, Fam WM: Regulation of coronary blood flow. Bull NY Med **42**: 940, 1966
6. Olsson RA: Myocardial reactive hyperemia. Circ Res **37**: 263, 1978
7. Koberstein RC, Pittman DC, Klocke FJ: Right atrial admixture in coronary venous blood. Am J Physiol **216**: 531, 1969
8. Lucchiari PH, Feofiloff EF, Boscardim AT, Bacila M: A technique for the determination of the available oxygen in living carp (Cyprinus Carpio) muscle. Comp Biochem Physiol **78A**: 675, 1984
9. Connelly CM: Methods for measuring tissue oxygen tension: theory and evaluation: the oxygen electrode. Fed Proc **16**: 681, 1957
10. Kreuzer F, Nessler CG Jr: Method of polarographic in vivo continuous recording of blood oxygen tension. Science Washington **128**: 1005, 1958
11. Whalen WJ, Riley J, Nair P: A microelectrode for measuring intracellular PO_2. J Appl Physiol **23**: 798, 1967
12. Kolmer HHB, Kreuzer F: Continuous polarographic recording of oxygen pressure in respiratory air. Resp Physiol **4**: 107, 1968

13. Davies PW, Brink F Jr: Microelectrodes for measuring oxygen tension in animal tissues. Rev Scient Instrum **13**: 524, 1942
14. Sayen JJ, Sheldon WF, Horwitz O, Kuo PT, Peirce G, Zinsser HF, Mead J Jr: Studies of coronary disease in the experimental animal. II. Polarographic determinations of local oxygen availability in the dog's left ventricle during coronary occlusion and pure oxygen breathing. J Clin Invest **30**: 932, 1951a
15. Sayen JJ, Zinsser HF, Kuo PT, Horwitz O, McCallie DF: Studies of coronary disease in the experimental animal. III. Polarographic studies of intramyocardial oxygen availability in dog with acute coronary occlusion and narrowing correlated with epicardial electrocardiograms. J Clin Invest **30**: 670, 1951b
16. Sayen JJ, Sheldon WF, Peirce G, Kuo PT: Polarographic oxygen, the epicardial electrocardiogram and muscle contraction in experimental acute regional ischemia of the left ventricle. Circ Res **6**: 779, 1958
17. Sayen JJ, Katcher AH, Sheldon WF, Gilbert CM Jr: The effect of levarterenol on polarographic myocardial oxygen, the epicardial electrocardiogram and contraction. Circ Res **8**: 109, 1960
18. Jamieson D, van den Brenk HAS: Electrode size and tissue PO_2 measurement in rats exposed to air or high pressure oxygen. J Appl Physiol **20**: 514, 1965
19. Moss AJ: Intramyocardial oxygen tensions. Circulation **33/34** (suppl): 17, 1966
20. Whalen WJ: Intracellular PO_2 in heart and skeletal muscle. Physiologist Lond **14**: 69, 1971
21. Winbury MM, Howe BB, Weiss HR: Effect of nitroglycerin and dipyridamole on epicardial and endocardial oxygen tension-further evidence for redistribution of myocardial blood flow. J Pharmac Exp Ther **176**: 184, 1971
22. Angell CS, Lakata EG, Weisfeldt MR, Shock NW: Relationship of intramyocardial oxygen tension and epicardial ST segment changes following acute coronary artery ligation: effects of coronary perfuse pressure. Cardiovasc Res **9**: 12, 1975
23. Losse B, Schuchhardt S, Niederle N: The oxygen pressure histogram in the left ventricular myocardium of the dog. Pflügers Arch ges Physiol **356**: 121, 1975
24. Rink RD: The acute effects of nicotine, tobacco smoke and carbon monoxide on myocardial oxygen tension in the anaesthetized cat. Br J Pharmacol **62**: 591, 1978
25. Cater DB: Oxygen tension and oxidation-reduction potentials in living tissues. Prog Biophys **10**: 154, 1960
26. Cater DB, Silver IA, Wilson GM: Apparatus and technique for quantitative measurement of oxygen tension in living tissues. Proceedings of the Royal Society of London Biological Sciences, 151, 1960
27. Cobbold RSC: Transducer for the measurements of ions and dissolved gases. *in* Transducer for Biomedical Measurements: Principles and Applications, John Wiley & Sons, New York, p 323–411, 1974
28. Gamble WJ, LaFarge CG, Fyler DC, Weisul J, Monroe RG: Regional coronary venous oxygen saturation and myocardial oxygen tension following abrupt changes in ventricular pressure in the isolated dog heart. Circ Res **34**: 672, 1974
29. Monroe RG, Gamble WJ, LaFarge CG, Benoualid H, Weisul J: Transmural coronary venous O_2 saturations in normal and isolated hearts. Am J Physiol **228**: 318, 1975
30. Maekawa K, Yokoyama M, Katada Y, Ishikawa Y, Fujiwara K, Mizutani T, Fukuzaki H: A study on myocardial ischemia in the left ventricular wall with special reference to electrographic and metabolic changes. Jpn Heart J **21**: 215, 1980