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Research Article

HYPOXEMIA AND CORONARY BLOOD FLOW [1, 2]

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Hypoxemia has long been known to produce a decrease in resistance in the vascular system of the heart. From studies on the effect of hypoxemia on coronary blood flow in the dog heart-lung preparation, Hilton and Eichholtz (2) reached the conclusion that the decrease in coronary resistance produced by hypoxemia is due to a direct action of low arterial oxygen tension on the smooth muscle of the vessels. However, the evidence in support of this contention is indirect and does not exclude myocardial hypoxia as the initiating factor.

If it can be demonstrated that under certain experimental conditions, which exclude myocardial hypoxia, a reduction in coronary arterial oxygen content does not increase coronary blood flow, then it would appear doubtful that low arterial oxygen tension has a direct action on the smooth muscle of the coronary vessels. This report is concerned with experiments in which high coronary perfusion pressures were employed in an attempt to determine the effect of low arterial oxygen tension on the coronary vessels in the absence of myocardial hypoxia.

METHODS

I. Experiments on the intact beating heart

Eleven technically satisfactory experiments were performed on open-chest dogs anesthetized with pentobarbital (30 mgm. per Kg.).

Preparation. The chest was opened in the fourth left intercostal space and artificial respiration started. Following administration of heparin [3] the left common coronary artery was cannulated with an Eckstein cannula (3) and perfused from a carotid artery via a pump perfusion system (Figure 1). By means of this perfusion system any desired perfusion pressure could be obtained regardless of aortic pressure. The coronary sinus was cannulated and the sinus outflow routed to the right jugular vein. Coronary blood flow was measured by an optically recording rotameter (4). Perfusion pressure was kept constant by means of a screw clamp and an air outlet at the top of the reservoir and was measured at a point just proximal to the coronary cannula. Perfusion and aortic pressures were optically recorded by modified Gregg manometers.

Deoxygenation of blood. Arterial blood from the experimental animal was deoxygenated by passing it directly from a femoral artery through the lungs of a recently sacrificed dog whose lungs were intermittently inflated with 5 per cent CO_2 in nitrogen. Different degrees of desaturation could be obtained by varying the rate of blood flow through the lungs, varying the respiratory cycle in the isolated lungs, or altering the oxygen content of the gas used to inflate the isolated lungs. For control periods, femoral arterial blood was passed through lungs intermittently inflated with 5 per cent CO_2 in oxygen.

Experimental procedure. The deoxygenated or oxygenated arterial blood was pumped through tube A (Figure 1) into the reservoir, and thence through the system into the left coronary artery at constant perfusion pressures. Records of pressure and flow and samples of coronary artery and coronary sinus blood were obtained two minutes after perfusion with deoxygenated or oxygenated blood was started. Coronary blood flow and coronary sinus oxygen content were stabilized at this time. Analyses for oxygen content were done in duplicate by the method of Roughton and Scholander (5). Between experimental periods perfusion of the left coronary artery was maintained by clamping the tubing at A and unclamping at B (Figure 1). Arterial pressure was kept nearly constant in the experimental animal by means of a Lampson bottle connected to one femoral artery. At no time was there systemic hypoxia since artificial respiration with room air was continued throughout the experiment. At the conclusion of each experiment the perfused part of the heart was stained with India ink, excised and weighed.

II. Fibrillating heart preparation

In two experiments, a dog fibrillating heart preparation was employed and the left coronary artery was perfused. The fact that the right coronary artery was not perfused does not affect the results in these experiments, since 1) flows were compared at equal perfusion pressures during control and hypoxemia periods, and 2) collateral flow between right and left coronary arteries is less than one cubic centimeter of blood per minute (6).

[1] Supported by a grant from the Cleveland Area Heart Society.

[2] Published previously as a preliminary report (1).

[3] Kindly supplied by the Upjohn Company, Kalamazoo, Michigan.

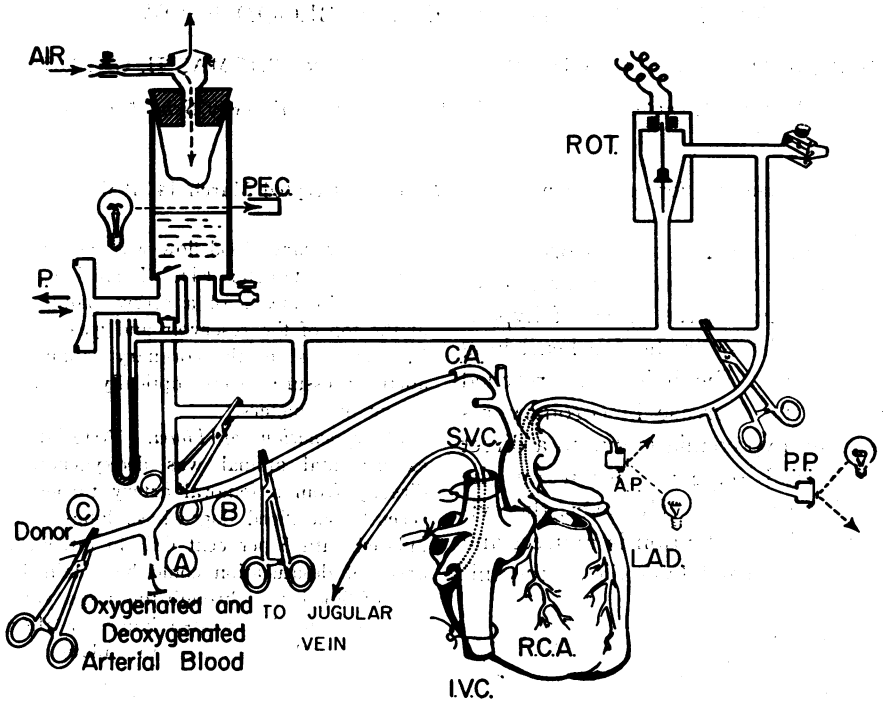

FIG. 1. DIAGRAM OF THE APPARATUS

P. = Modified Dale-Schuster pump; P.E.C. = Photoelectric cell with relay to start pump when level in reservoir falls; ROT. = Rotameter; C.A. = Carotid artery; S.V.C. = Superior vena cava; I.V.C. = Inferior vena cava; L.A.D. = Left anterior descending coronary artery; R.C.A. = Right coronary artery; P.P. = Perfusion pressure; A.P. = Aortic pressure.

The vena cavae and azygos vein were ligated and the main pulmonary artery was cannulated centrally. Between experimental periods blood from a donor dog perfused the left coronary artery via tube C (Figure 1) and was collected from the pulmonary artery and periodically returned to the donor. In these experiments the lungs of the experimental animal (fibrillating heart) were used for deoxygenating the donor dog's arterial blood in the same manner as for the experiments on the beating heart.

RESULTS

In the first two experiments (Table I), coronary artery perfusion pressure was set at 100 mm. Hg. In these experiments control coronary sinus oxygen was in the upper level of the normal range. However, when the coronary arterial oxygen content was reduced to approximately half the control values, the sinus oxygen content reached very low levels and coronary blood flow exhibited a large increase. Aortic pressure, heart rate, and myocardial oxygen consumption remained relatively constant.

In the third experiment, coronary artery perfusion pressure of 130 mm. Hg produced high coronary sinus oxygen levels when coronary arterial blood was fully saturated with oxygen. Reducing arterial oxygen content from 23.1 to 8.9 volumes per cent resulted in an increase in coronary flow and a reduction of coronary sinus oxygen content from 12.5 to 2.2 volumes per cent. It was only by virtue of the increment in blood flow that the myocardial oxygen supply was maintained. In periods 4 and 6 of Experiment 3 arterial oxygen content was reduced so drastically that the extraction of oxygen from blood perfusing the myocardium was almost complete. Despite the large increases in blood flow in periods 4 and 6 the cardiac oxygen supply was impaired and myocardial oxygen consumption fell below control levels.

In Experiments 4 and 5, control coronary sinus oxygen contents were within the normal range and the increments in coronary blood flow

TABLE I

Effect of reduction in arterial oxygen content on coronary blood flow at different perfusion pressures

Exp. No.	CBF	Perfusion pressure	Arterial O_2	Coronary sinus O_2	O_2 cons.	Heart rate	Aortic pressure
	cc./min./100 gm.	*mm. Hg*	*vol. %*	*vol. %*	*cc./min./100 gm.*	*beats/min.*	*mm. Hg*
1	80	98	21.1	9.2	9.5	180	119/98
	113	102	11.3	3.3	9.0	170	130/104
	84	96	19.1	7.8	9.5	170	120/96
2	55	102	21.1	6.4	8.1	156	122/108
	95	100	12.1	2.8	8.8	156	122/107
	62	97	21.3	8.0	8.3	156	122/108
	109	93	9.7	1.6	8.8	156	124/105
	62	104	22.1	8.3	8.6	156	126/110
	111	97	9.9	1.7	9.2	156	121/101
	74	102	20.6	8.5	9.0	156	119/105
3	65	133	23.1	12.5	6.9	120	130/97
	89	126	8.9	2.2	6.0	120	139/113
	57	129	22.7	12.0	6.1	120	137/116
	106	128	4.9	1.0	4.1	120	146/116
	69	131	24.3	15.6	6.0	120	130/110
	107	128	5.2	0.9	4.6	120	154/120
4	119	139	17.6	8.4	13.3	150	128/114
	157	136	8.9	2.1	10.7	180	145/128
	112	138	16.2	5.6	11.9	180	134/118
	157	138	8.1	2.0	9.6	150	134/118
	133	140	15.4	4.2	14.9	180	134/118
5	103	158	16.7	6.4	10.6	165	148/121
	127	158	11.9	4.3	9.6	150	150/122
	112	160	17.4	7.1	11.5	150	152/124
	130	161	13.1	4.6	10.1	150	158/127
	127	159	17.2	7.8	11.9	150	150/120
	149	161	8.1	2.4	8.5	150	157/124
6	101	154	19.4	9.1	10.4	195	140/104
	106	158	16.6	8.2	8.9	195	140/104
7	144	160	20.1	16.7	4.9	145	113/79
	154	160	12.7	9.6	4.8	135	114/81
	153	160	20.0	16.8	4.9	130	112/80
8	126	191	21.7	14.8	8.7	170	121/99
	128	194	19.2	12.3	8.9	165	125/100
	138	196	18.0	11.4	9.1	150	129/101
	129	200	22.0	16.8	6.7	145	125/98
	139	200	13.4	8.2	7.2	140	129/100
9	117	152	20.5	13.6	8.1	135	129/91
	117	150	16.5	9.6	8.1	130	141/101
	104	153	20.4	13.0	7.7	140	147/102
	104	150	17.2	10.4	7.1	140	135/101
	107	150	20.5	13.1	7.9	140	125/93
10	133	176	14.0	5.9	10.8	190	139/110
	134	179	18.6	10.1	11.2	180	140/109
	138	178	14.0	6.2	10.8	180	145/114
	136	179	18.5	11.7	9.0	165	133/101
	139	179	13.2	6.0	10.0	165	141/106
11	122	180	24.3	14.7	11.7	180	120/95
	123	180	21.0	11.3	11.9	180	124/98
	118	180	18.4	8.8	11.3	180	114/90
12	131	111	17.0	13.4	4.7	Vent.	
	122	111	13.7	10.0	4.5	Fib.	
13	208	161	14.2	12.0	4.6	Vent.	
	196	159	12.5	10.3	4.3	Fib.	
	204	163	12.0	9.9	4.3		
	218	159	10.9	8.9	4.4		

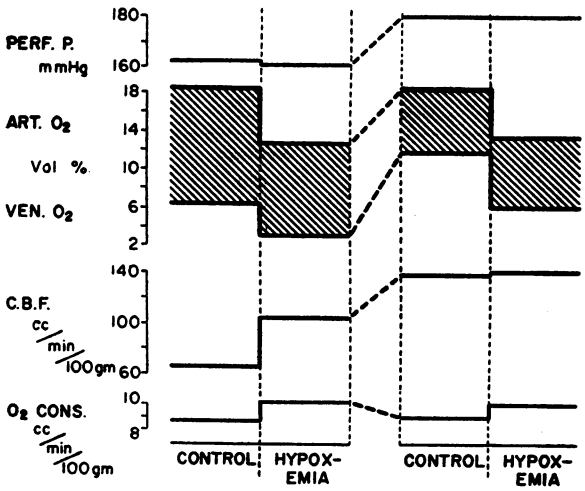

FIG. 2. EFFECT OF HYPOXEMIA ON CORONARY BLOOD FLOW AT TWO DIFFERENT PERFUSION PRESSURES

were roughly proportional to the reduction in coronary sinus oxygen content observed.

In Experiments 6 through 13, high coronary sinus oxygen levels were maintained during control periods by employing a high perfusion pressure. With moderate decreases in arterial oxygen content coronary blood flow remained relatively constant and coronary sinus oxygen content did not fall below 5.9 volumes per cent. Myocardial oxygen consumption, aortic pressure, and heart rate showed little change.

The importance of the oxygen supply to the myocardium, as reflected by the level of coronary sinus oxygen content, is illustrated in Figure 2, in which the effect of alterations in arterial oxygen content on coronary blood flow is seen in the same animal at different perfusion pressures. At a pressure of 160 mm. Hg and arterial oxygen content of 18.5 volumes per cent, coronary sinus oxygen content was 6.3 volumes per cent and coronary blood flow was 70 cc. per minute per 100 grams of heart muscle. When arterial blood containing 12.6 volumes per cent of oxygen was infused into the left coronary artery at the same pressure, coronary sinus oxygen content was reduced to 2.8 volumes per cent and flow rose to 105 cc. per minute. In the second half of the experiment, perfusion pressure was increased to 180 mm. Hg and at a control arterial oxygen level of 18.5 volumes per cent coronary flow was 136 cc. per minute and coronary sinus oxygen content 13.2 volumes per cent. When the arterial oxygen content was reduced to 11.7 volumes per cent at this higher perfusion pressure, coronary sinus oxygen content decreased to 6.0 volumes per cent and no significant change in coronary blood flow occurred.

The relationship between coronary blood flow and the oxygen content of venous blood is depicted for all experiments in Figure 3. The points represent the cardiac venous blood oxygen content during coronary perfusion with partially desaturated arterial blood plotted against the observed change in coronary blood flow. No change in coronary blood flow occurred at coronary sinus oxygen levels greater than 5.5 volumes per cent. However, below this point a direct relationship appears to exist between the reduction in coronary sinus oxygen content and the increase in coronary blood flow.

The absence of a direct relationship between arterial oxygen content and coronary blood flow is illustrated by Figure 4, in which arterial oxygen content of partially desaturated blood perfusing the coronary artery is plotted against the change in coronary blood flow observed during the infusion period. In Figure 4 the solid circles represent arterial oxygen values in experimental periods when coronary sinus oxygen was greater than 5.5 volumes per cent and the open circles when coronary sinus oxygen was below 5.5 volumes per cent. In the range of arterial oxygen content (10 to 15 volumes per cent), in which there is overlap of venous oxygen levels above and below 5.5 volumes per cent, all the points representing the higher coronary sinus oxygen levels are clustered about zero flow change, whereas points representing the lower sinus oxygen levels (at the same arterial oxygen level) are associated with increases in coronary blood flow.

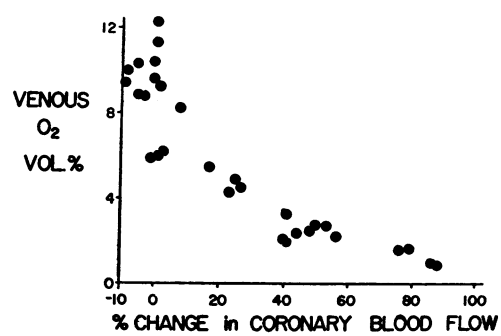

FIG. 3. RELATIONSHIP OF CORONARY SINUS BLOOD OXYGEN CONTENT TO CORONARY BLOOD FLOW

See text for discussion.

DISCUSSION

A reduction in the oxygen content of blood perfusing the coronary arteries and arterioles has no direct effect upon resistance within the vasculature of the heart, provided that the myocardium receives an adequate supply of oxygen. The fact that coronary blood flow increased when coronary sinus oxygen content fell below 5.5 [4] volumes per cent, regardless of the arterial oxygen content, suggests a causal relationship between venous oxygen content and coronary resistance in hypoxemia. A similar correlation has been found by Katz, Katz, and Williams (7). Since it is unlikely that dilation of venules or veins can produce reductions in coronary resistance of the order of magnitude observed in the present studies, and since venous oxygen content closely reflects tissue oxygen content, the coronary dilation of hypoxemia can probably be ascribed to reductions in oxygen content within the myocardium. This relative myocardial hypoxia could result in the local release of vasoactive metabolites, an idea that has been considered for over half a century. If arterial oxygen content is the primary factor responsible for resistance changes in the coronary circulation, then reduction in arterial oxygen content should have been equally effective in decreasing coronary resistance at different levels of oxygen within the myocardium.

Nervous and humoral mechanisms originating outside the heart have been eliminated in the present studies, since in the whole animal experiments only blood entering the left coronary artery was made hypoxic and in the fibrillating heart experiments a completely isolated heart was used. Alella (8) and Hackel and Clowes (9), who have observed marked increases in coronary blood flow in generalized hypoxia, found that cardiac denervation and/or adrenalectomy did not influence the response of the coronary vessels to hypoxia.

In 1925, Hilton and Eichholtz (2) challenged the hypothesis of the release of vasodilator substances during hypoxia and periods of increased myocardial metabolism and attributed the increased coronary flow of hypoxemia to a direct effect of the lowered arterial oxygen tension on the vessel walls. Their conclusions were based on the findings that 1) perfusion of the coronary arteries with fresh metabolite-free deoxygenated arterial blood or the intra-coronary administration of cyanide produced immediate increases in coronary blood flow, 2) myocardial oxygen consumption did not decrease with hypoxemia, 3) high concentrations of carbon dioxide and lactic acid produced only small increases in coronary flow, and 4) the progressive coronary vasodilation observed in the heart-lung preparation was not corrected by replacing the blood in the system with fresh blood. They also cited, as evidence against the "metabolite theory," experiments of Nakagawa (10) and Evans (11) in which increases in heart rate and cardiac output in the heart-lung preparation were attended by increases in oxygen consumption without concomitant increments in coronary blood flow.

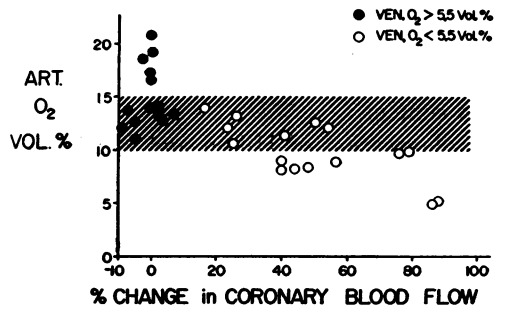

FIG. 4. RELATIONSHIP OF ARTERIAL BLOOD OXYGEN CONTENT TO CORONARY BLOOD FLOW
See text for discussion.

The rapidity of the response to fresh deoxygenated blood or to cyanide does not eliminate the possibility that vasoactive metabolites are released. Due to the large oxygen consumption and the high coefficient of utilization of oxygen in the normal beating heart, a sudden decrease in oxygen supply would produce an equally rapid reduction in myocardial oxygen tension. Since diffusion rates for substances of small or moderate molecular weights are high (12), it is quite conceivable that vasoactive materials released as a result of myocardial hypoxia could quickly reach the arterioles in effective concentrations.

The maintenance of myocardial oxygen consumption in hypoxemia could be attributed with equal justification to vasodilation induced by metabolites or to vasodilation induced by direct action of reduced arterial oxygen content on the vessel walls. There is no valid reason to exclude the possibility that vasoactive material released by

[4] Average value for coronary sinus oxygen in the normal dog (6).

hypoxic myocardium, in the presence of normal rates of myocardial oxygen consumption, adjusts flow to compensate for the reduction in arterial oxygen content.

The observation of Hilton and Eichholtz (2), that concentrations of carbon dioxide and lactic acid in excess of those found in venous blood during hypoxia failed to produce vasodilation equal to that seen in hypoxia, merely indicates that these two substances are not the only chemical mediators acting on the coronary vessels. It does not exclude other metabolites. Nor does the failure of fresh blood to reverse the progressive coronary dilation in the heart-lung preparation eliminate metabolites as playing a role in the vasodilation of hypoxemia.

Concerning the experiments of Nakagawa (10) and of Evans (11), it has now been firmly established in intact dogs, using precise methods for measuring flow, that coronary blood flow bears a direct relationship to myocardial oxygen consumption (13–15). In fact, this is the one function that can be consistently related to coronary blood flow, regardless of the means by which the rate of myocardial metabolism is increased.

The close correlation between myocardial oxygen consumption and coronary blood flow, the direct relationship between the duration of cardiac ischemia and the degree of reactive hyperemia (16), and the observations that reductions in arterial oxygen content in the absence of myocardial hypoxia do not increase coronary blood flow suggest that myocardial oxygen content and not arterial oxygen content is the critical factor in the regulation of coronary blood flow. Whether a decrease in myocardial oxygen content results in release of vasodilator substances remains to be proven.

SUMMARY

In experiments on open-chest dogs and on fibrillating heart preparations, reduction of oxygen content of arterial blood produced increases in coronary blood flow only when coronary sinus oxygen levels fell below about 5.5 volumes per cent. High perfusion pressures were employed in order to increase coronary flow to the extent that coronary sinus blood became relatively rich in oxygen. Under these conditions it was possible to demonstrate that a moderate lowering of arterial oxygen content does not decrease coronary resistance by a direct action on the vessel walls. Coronary vasodilation in hypoxemia appears to be related to myocardial hypoxia.

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