PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 165, 264–270 (1980)

Coronary Vascular Resistance during Hypocapnia in the Closed-Chest Dog (40968)[1]

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Abstract. Coronary vascular resistance during whole-body hypocapnia was studied in anesthetized dogs in which coronary blood flow (CBF) was monitored from a catheter-tip flow meter. Intravascular placement of this flow meter did not require opening the chest and avoided possible coronary denervation. Rapid flow meter response permitted determination of coronary vascular resistance during late diastole when vascular compression during systole does not affect the calculation. With rate and depth of ventilation held constant, hypocapnia was induced by a rapid change of the ventilating gas from 95% O_2–5% CO_2 to 100% O_2. Within 30 sec of the change to 100% O_2 and prior to any change in mean arterial blood pressure (AP), late diastolic coronary vascular resistance (LDR) decreased from 2.04 ± 0.26 to 1.44 ± 0.20 mm Hg/ml/min. LDR remained below control throughout the hypocapnic period while AP decreased from 122 ± 7 to 111 ± 7 mm Hg and CBF was unchanged. β-Adrenergic blockade with propranolol eliminated the decrease in LDR seen during hypocapnia prior to block, AP was unchanged, and CBF decreased from 36 ± 8 to 27 ± 7 ml/min. The decrease in LDR during hypocapnia was reversed following combined α- and β-adrenergic blockade with propranolol plus dibenamine and LDR increased from 0.90 ± 0.14 to 2.27 ± 0.85 mm Hg/ml/min. After combined block, CBF decreased from 78 ± 8 to 53 ± 8 ml/min by 3 min of hypocapnia and AP increased from 84 ± 19 to 108 ± 16 mm Hg by the end of the hypocapnic period. The increase in heart rate observed late in the hypocapnic period persisted following β block but was eliminated following combined blockade. These data suggest that adrenergic effects during whole-body hypocapnia may initially offset a local coronary vasocontriction which is unmasked following combined α- and β-adrenergic blockade.

The coronary vascular response to hypocapnia or hypocapnic alkalosis is not settled. Clinical (1) and other studies (2–4) suggest that coronary blood flow (CBF) is either unchanged or reduced by procedures such as hyperventilation that lower arterial P_{CO_2} and raise pH. However, these observations were accompanied by changes in heart rate (HR) and arterial blood pressure which also affect CBF. Vascular responses may have been obscured by passive changes in vessel caliber due to myocardial compression. Furthermore, in the animal experiments, partial surgical denervation of the coronary vessels may have occurred during placement of flow probes. These objections have been partially satisfied in the study reported here. The data presented below show a decrease in coronary vascular resistance prior to a change in arterial pressure in response to rapidly induced, short-term whole-body hypocapnia in the anesthetized dog instrumented with a catheter-tip coronary flow meter (5). This response was eliminated following β-adrenergic blockade and reversed following combined α- and β-adrenergic blockade.

Methods and materials. Dogs (22–30 kg) premedicated with morphine sulfate (30 mg sc) were anesthetized with urethane (0.50 g/kg) and α-chloralose (0.075 g/kg) iv, intubated, and ventilated. CBF was monitored from a velocity-sensitive catheter-tip flow meter inserted through the right carotid artery with the tip positioned in the circumflex or anterior descending branch of the left common coronary artery. Flow meter position was determined by characteristics of the flow pulse and by the hyperemic response following brief occlu-

[1] Grant support from Central Ohio Heart Chapter, American Heart Association.

0037-9727/80/100264-07$01.00/0

sion of the vessel by closure of a flow meter valve. Position was confirmed at autopsy. Zero flow was determined by flow meter valve occlusion. The flow meter was calibrated with fresh dog blood. Aortic pressure was monitored from a catheter-tip manometer (6) positioned via the brachial artery. Central venous pressure (CVP) was monitored via a femoral vein catheter with the tip positioned in the chest. The electrocardiogram (ECG) was recorded from a standard limb lead. Cardiac output ($\dot{Q}$) was determined by the Stewart–Hamilton indicator-dilution technique. A right heart catheter was inserted via the jugular vein and indocyanine green was automatically injected at the same time in the respiratory cycle. Blood was withdrawn at a constant rate from an aortic catheter inserted via a femoral artery and was passed through a densitometer before return to the animal. A computer (7) was used to integrate the dye concentration curves and calculate $\dot{Q}$. Data were simultaneously recorded on paper and stored on electromagnetic tape.

End-expiratory CO_2 was monitored from an infrared gas analyzer and was maintained at 5% by ventilation with 95% O_2–5% CO_2 during control periods. Rate and depth of ventilation were constant throughout the experimental sequence: 20 min control, 8 min hypocapnia, 20 min control. Hypocapnia was induced in 11 dogs by a rapid change of the ventilating gas to 100% O_2. Eight of the eleven dogs were subjected to a repeat 8-min hypocapnia following either β-adrenergic blockade with propranolol (1 mg/kg iv), $n = 4$, or combined α- and β-adrenergic blockade with propranolol (1 mg/kg iv) plus dibenamine (20 mg/kg iv), $n = 4$. Isoproterenol (0.5 μg/kg iv) was given before and again after propranolol to test the effectiveness of the block.

Pressure and flow data were analyzed during control and at 30 sec and 3, 5, and 8 min during hypocapnia. Blood samples for P_{CO_2} and pH were drawn periodically. $\dot{Q}$ was determined within 3 min of gas changes in four dogs.

CBF was obtained by planimetry of the area under the flow–time curve over at least four CBF pulses. Area divided by the time interval over which it was determined was translated into CBF through use of calibration curves.

Calculation of coronary vascular resistance during late diastole eliminated the effect of systolic myocardial compression on vessel caliber. Panerai *et al.* (8) recently showed a linear relationship between aortic pressure and CBF during diastole. Pressure and flow values coincident with the R wave of the ECG were obtained over at least four successive heartbeats and late diastolic coronary vascular resistance (LDR) was calculated by dividing pressure by flow. The R wave was chosen as a late diastolic reference because its correspondence with pressure and flow patterns appeared independent of HR. Mean arterial blood pressure (AP) was computed as one-third systolic + two-thirds diastolic aortic pressure.

Analysis of variance for repeated measures followed by the Dunnett t test was used to determine the statistical significance of differences between control and hypocapnic values. Student's paired t test was used to compare control values before and after blockade. Significance was accepted at a $P \leq 0.05$. Data are expressed as mean ± SEM.

Results. Arterial blood pH increased from 7.26 ± 0.006 to 7.44 ± 0.003 within 30 sec of hypocapnia. By 3 min, pH reached 7.52 ± 0.015 and remained at this level throughout the rest of the hypocapnic period. On return to 95% O_2–5% CO_2, pH declined to 7.28 ± 0.011 within 4 to 6.5 min and to 7.27 ± 0.014 within 18 to 33 min of recovery. End-expiratory CO_2 was 2–3% during hypocapnia. Within 8 min of the gas change to 100% O_2, P_{CO_2} decreased significantly from a control of 41 ± 4 to 17 ± 1 ($P < 0.025$, $n = 5$). Recovery samples were obtained from three of these dogs and arterial P_{CO_2} averaged 38 ± 2.

AP, CVP, and HR varied an average of 6% over the 5 min prior to all hypocapnic sequences and control values were those obtained just prior to hypocapnia. CBF was less stable and tended to rise or fall slowly during the control period in many experiments. CBF variability during the previous

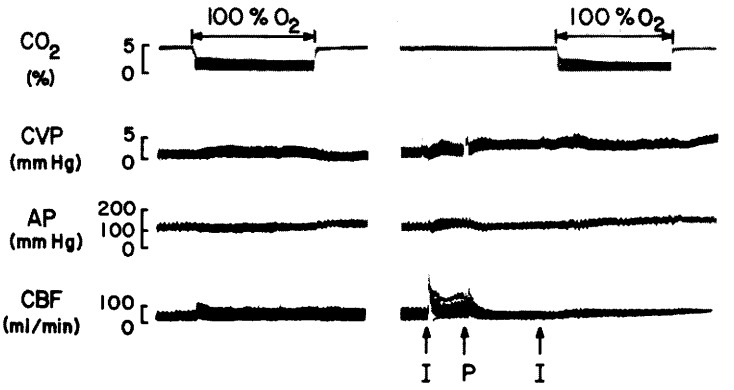

FIG. 1. Representative record and measurements in one animal during 8-min hypocapnia (100% O_2) before and after β-adrenergic blockade with propranolol (P). Traces: expired CO_2, central venous pressure (CPV), arterial pressure (AP) and coronary blood flow (CBF). I = isoproterenol.

control period did not seem to affect the direction of the CBF change during hypocapnia.

Hypocapnia. Figure 1 shows a representative record obtained from an experiment in which the dog was subjected to a hypocapnic period before and again after β-adrenergic blockade. The top trace shows the rapidity of the change in expired CO_2 accompanying the ventilatory gas change. In the bottom trace, a marked increase in CBF is apparent at the beginning of the first hypocapnic period at a time when AP appears to be falling.

The average of responses to hypocapnia in 11 nonblocked dogs are shown in Table I. LDR decreased significantly within 30 sec of the change to 100% O_2. The increase in HR and the decrease in AP were significant by 3 min of hypocapnia while CBF and CVP were not significantly changed. $\dot{Q}$ averaged 1.74 ± 0.39 prior to and 2.21 ± 0.68 liters/min (n = 4) within 3 min of the onset of hypocapnia but these values are not significantly different. Within 4 to 8 min of the return to 95% O_2–5% CO_2, AP and HR were no longer significantly different from previous control values. Similar changes were seen when the hypocapnic period was repeated after 9.0 ± 1.4 min in 3 dogs.

Hypocapnia following β-adrenergic blockade. The marked increase in CBF associated with isoproterenol prior to β blockade was completely eliminated following propranolol (Fig. 1). All four blocked dogs met the criterion for effective β blockade: absence of an increase in CBF in response to isoproterenol. β blockade significantly reduced AP (Table I).

Figure 1 shows that the transient increase in CBF observed during hypocapnia in this animal prior to β block was absent following propranolol. The average of responses to hypocapnia following β blockade are seen in Table I. In contrast to the decrease in LDR associated with hypocapnia prior to β blockade, LDR did not decrease during hypocapnia following blockade. AP did not change while HR increased significantly at 5 min. Both CBF and CVP decreased significantly during hypocapnia. $\dot{Q}$ increased significantly from a control value of 1.69 ± 0.36 to 1.89 ± 0.33 liters/min (n = 3) within the first 3 min of hypocapnia. An interval of 16.3 ± 5.4 min separated the pre- and post-blockade hypocapnic periods.

Hypocapnia following combined α- and β-adrenergic blockade. Combined α and β blockade significantly decreased both baseline LDR and AP (Table I). Figure 2 is a representative record of the response to hypocapnia in the same animal before (A) and again after (B) combined α- and β-adrenergic blockade. The marked rise in CBF seen during the first minute of hypocapnia in this record prior to block was greatly attenuated following blockade in spite of an accompanying rise in AP.

TABLE I. RESPONSE TO HYPOCAPNIA IN DOGS UNDER CONDITIONS OF NO BLOCK (n = 11), β-ADRENERGIC BLOCKADE (n = 4), AND α- AND β-ADRENERGIC BLOCKADE (n = 4)

		Hypocapnia				
	Condition	Control	30 sec	3 min	5 min	8 min
LDR[a] (mm Hg/ml/min)	No block	2.04 ± 0.26[b]	1.44 ± 0.20[c]	1.64 ± 0.22[c]	1.63 ± 0.23[c]	1.67 ± 0.25[c]
	β block	3.28 ± 1.11	3.38 ± 1.31	4.08 ± 1.82	4.92 ± 2.48	4.04 ± 1.63
	α + β block	0.90 ± 0.14[d]	1.19 ± 0.28	2.27 ± 0.85[c]	2.18 ± 0.68[c]	2.02 ± 0.43
CBF (ml/min)	No block	65 ± 11	86 ± 20	62 ± 12	70 ± 13	70 ± 14
	β block	36 ± 8	37 ± 9	33 ± 8	29 ± 7	27 ± 7[c]
	α + β block	78 ± 8	64 ± 3	53 ± 8[c]	47 ± 7[c]	42 ± 4[c]
AP (mm Hg)	No block	122 ± 7	115 ± 7	111 ± 7[c]	112 ± 7[c]	116 ± 8
	β block	114 ± 5[d]	116 ± 5	116 ± 6	118 ± 6	120 ± 6
	α + β block	84 ± 19[d]	95 ± 22	103 ± 24	112 ± 16[c]	108 ± 16[c]
HR (beats/min)	No block	135 ± 12	146 ± 11	172 ± 13[c]	170 ± 12[c]	167 ± 13[c]
	β block	105 ± 14	110 ± 13	117 ± 12	122 ± 13[c]	116 ± 11
	α + β block	135 ± 10	136 ± 12	138 ± 14	142 ± 12	143 ± 10
CVP (mm Hg)	No block (n = 8)	4.4 ± 1.6	4.3 ± 1.7	4.3 ± 1.5	4.4 ± 1.6	4.3 ± 1.6
	β block (n = 3)	4.8 ± 2.0	4.8 ± 1.8	4.0 ± 2.1[c]	4.2 ± 1.9[c]	4.5 ± 1.9
	α + β block (n = 3)	3.7 ± 1.2	2.8 ± 0.7	2.2 ± 1.1	2.2 ± 0.6	2.5 ± 0.3

[a] LDR, Late diastolic coronary vascular resistance; CBF, coronary blood flow; AP, arterial pressure; HR, heart rate; CVP, central venous pressure.
[b] All values are mean ± SEM.
[c] Significantly different from control.
[d] Significantly different from no block.

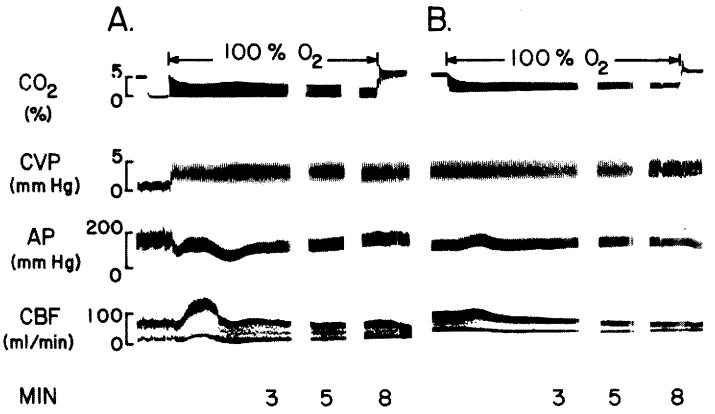

FIG. 2. Representative record of measurements in the same animal during hypocapnia before (A) and after (B) combined α- and β-adrenergic blockade with propranolol and debenamine. The CO_2 meter zero was checked and the sensitivity of the CVP amplifier was increased just prior to the first hypocapnic period (CVP scale applies to the greater sensitivity).

Average data from four dogs (Table I) show that, following combined α and β blockade, measured variables did not change until 3 min of hypocapnia after which the increase in LDR and AP and the decrease in CBF were significant. HR and CVP did not change. The pre- and post-blockade hypocapnic periods were 26.8 ± 1.5 min apart.

Discussion. The Pieper coronary flow meter in our study offers several advantages over methods used to determine CBF during hypocapnia in previous studies. The Pieper flow meter provides a pulsatile output of flow velocity making possible the calculation of LDR. LDR is not affected by passive changes in vessel caliber due to differences in myocardial compression as the strength of cardiac contraction varies. Instantaneous blood flow changes could be observed on introduction of hypocapnia because the response of the Pieper flow meter is much more rapid than flow determination methods such as ^{131}I-aminopyrine uptake in the study of Scheuer (9), nitrous oxide saturation in the study of Rowe (3), and ^{133}Xe clearance in the studies of Alexander (2) and Vance (10). Furthermore, placement of this catheter-tip flow meter does not require chest surgery with isolation and possible denervation of the coronary vessel.

Rapidly induced, whole-body hypocapnia of 8-min duration in our study was associated with a decrease in LDR which was maintained throughout the hypocapnic period. The decrease in LDR preceded a change in AP. β-Adrenergic blockade eliminated the decrease in LDR during hypocapnia. The time between hypocapnic periods is probably not a factor in the elimination of the decrease in LDR following β blockade since the vasodilation was present in three dogs in which no blocking drugs were given and the time between hypocapnic periods was even more brief. After combined α and β blockade, hypocapnia was associated with a significant increase in LDR. Combined α and β blockade markedly decreased control LDR and it might be argued that the coronary vessels were maximally dilated, thus no decrease in LDR could be evoked during hypocapnia. However, there is no reason to believe that the previously dilatory stimulus would then produce a constriction.

Whole-body hypocapnia generally has been reported to decrease CBF (2, 9–11). However, in several of these studies (2, 9, 11) mean coronary vascular resistance (CVR) computed as the ratio of the difference between AP and right atrial pressures to CBF may have been unchanged since both CBF and AP decreased. For example, calculation of CVR using the figures reported by Alexander (2) for CBF and AP

prior to and 20 min following hypocapnia indicates the CVR actually decreased from 1.22 to 0.96 during hypocapnia if right atrial pressure was unchanged. Rowe *et al.* (3) noted that hyperventilation in dogs results in no change in AP and CBF tends to remain the same or rise slightly but not significantly. Conversely, hyperventilation in healthy man in Rowe's study slightly decreased both AP and CBF. A decrease in CVR might not have been observed in these experiments because the change in arterial P_{CO_2} may have been slow. Kontos (12) observed in the forearm that the vasodilator phase of the response to hypocapnia was absent when the change in arterial P_{CO_2} was not rapid.

Hypocapnia has an initial vasodilator effect on limb blood vessels (12–15). Kontos (12) attributed the initial 4-min vasodilation of limb vessels to release of histamine, since vasodilation was accompanied by increased blood histamine concentration and was inhibited or reversed by antihistamines. β-Adrenergic blockade (14, 15) or combined α- and β-Adrenergic blockade (12) significantly reduced but did not eliminate hypocapnic vasodilation in limb blood vessels. Since propranolol completely blocked the decrease in LDR associated with hypocapnia in our study, it may be that adrenergic activity is more important in the vascular response to hypocapnia in the heart than in limb blood vessels.

After a transient dilation (4), local hypocapnia in the pump-perfused dog heart has been shown to increase CVR as indicated by a rise in coronary artery pressure at constant blood flow (4, 16, 17). Since hypocapnia in our study was associated with vasoconstriction in the α- and β-blocked dogs and vasodilation in the nonblocked dogs, it may be that a local vasoconstrictor effect of hypocapnia was reversed by adrenergic activity secondary to systemic hypocapnia in the nonblocked dogs.

The effect of hypocapnia on myocardial oxygen consumption ($M\dot{V}_{O_2}$) is unsettled. Vance *et al.* (10) found no change in $M\dot{V}_{O_2}$ during 20- to 30-min periods of whole-body hypocapnia in dogs. During hypocapnia in the working heart pump perfused at constant flow, Case *et al.* (16) found no change in aortic pressure, HR, or $M\dot{V}_{O_2}$ during hypocapnia. However, in the paced dog heart doing no pressure or volume work and pump perfused at constant flow, Harken and Woods (18) found an increase in $M\dot{V}_{O_2}$ with hypocapnia. The reason for the discrepancy between the findings of the latter two groups is not clear. During local hypocapnia, Daugherty *et al.* (4) observed a 66% increase in cardiac contractile force at the time of transient coronary vasodilation. It cannot be determined from our study whether the decrease in LDR we observed during hypocapnia in the nonblocked dogs was secondary to increased cardiac metabolism.

Summary. Rapidly induced, short-term whole-body hypocapnia decreased late diastolic coronary vascular resistance prior to any measurable effect on mean arterial pressure. This decrease in resistance was eliminated by β blockade. Following combined α and β blockade, hypocapnia was associated with an increase in late diastolic coronary vascular resistance indicating that adrenergic effects during whole-body hypocapnia may initially offset local coronary vasoconstriction.

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Received September 27, 1979. P.S.E.B.M. 1980, Vol. 165.