Control of Myocardial Oxygen Tension by Sympathetic Coronary Vasoconstriction in the Dog

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ABSTRACT

The effect of sympathetic alpha-receptor coronary vasoconstriction on myocardial oxygen tension was studied in open- and closed-chest, chloralose-anesthetized dogs. Blood oxygen tension in the coronary sinus and blood flow in the circumflex coronary artery were continuously measured in a three-part experiment. With stimulation of the left stellate ganglion (15 Hz, 3 msec, 4-7 v, 90-second train) under vagotomy control conditions (part 1), heart rate, blood pressure, and coronary blood flow increased, but coronary sinus oxygen tension decreased from 19 mm Hg to 15 mm Hg. In part 2, beta-receptor blockade with propranolol (2.0 mg/kg, iv) in the same dogs blunted the positive inotroic and chronotropic effects of sympathetic stimulation; coronary alpha-receptor vasoconstriction was unmasked, and coronary sinus blood oxygen tension fell from 17 mm Hg to 11 mm Hg. Since increases in oxygen metabolism were blunted, it appeared that the decrease in coronary sinus oxygen tension was caused by alpha-receptor coronary artery vasoconstriction. This hypothesis was tested in part 3 by the addition of alpha-receptor blockade with Dibozane (3.0 mg/kg, iv). Sympathetic stimulation no longer resulted in a change in either coronary vascular resistance or coronary sinus oxygen tension. These results indicate that the fall in oxygen tension during beta-receptor blockade in part 2 was due to alpha-receptor coronary vasoconstriction. Thus, myocardial oxygen tension may be regulated by coronary sympathetic vasomotion as well as by myocardial oxygen metabolism and local vascular control mechanisms.

Direct coronary vasoconstriction resulting from sympathetic stimulation has been demonstrated in several laboratories (1–10) and identified to be of the alpha-receptor type (4, 5). The objective of the present study was to determine whether sympathetic alpha-receptor coronary vasoconstriction is capable of modulating myocardial oxygen tension. A three-part experiment indicated that sympathetic alpha-receptor coronary vasoconstriction decreased coronary sinus oxygen tension.

Methods

GENERAL PREPARATION

Twenty-one dogs (21–34 kg) were studied. Each dog was anesthetized with alpha-chloralose (100 mg/kg, iv); supplemental doses were given as needed. Metabolic acidosis during anesthesia was combated by an intravenous infusion of 150 ml sodium bicarbonate (approximately 5 ml/kg hour−1) (11). The dog's temperature was maintained at 39°C.

The lungs were ventilated with a positive-pressure respirator (Harvard model 607). Atelectasis was prevented by maintaining an expiratory pressure of 5 cm H2O with a trap and occasional double inflation of the lungs by occluding the expiratory tube for one cycle.

End-expiratory carbon dioxide was measured continuously with an infrared absorption analyzer (Beckman LB-1) and kept between 4% and 5% by adjustment of the ventilation rate and the tidal volume (12). The dogs were ventilated with room air enriched with 40% oxygen in nitrogen via a variable-demand valve on the inlet side of the respiration pump. These two arrangements permitted semi-independent adjustment of end-expiratory carbon dioxide and arterial oxygen tension. At the completion of surgery, the level of anesthesia was checked, an additional dose of anesthetic was given, and the dogs were curarized with 1.5 mg/kg of Flaxedil (Davis & Geck), which permitted smooth ventilation control with the respirator. The dogs were then anticoagulated with an initial administration of 750 units of heparin and supplemental hourly doses of 250 units/kg.

Blood pressure was measured in the ascending aorta with a polyethylene catheter and a strain-gauge pressure transducer (Statham P23Dd). Mean arterial blood pressure was recorded by electronic integration with a 2.0-second time constant. Heart rate was continuously measured with a cardiotachometer triggered from the aortic pressure wave.

In seven dogs the pericardium was opened, in seven other dogs the pericardium was kept intact, and in seven other dogs the chest was kept closed. Otherwise all groups received the same treatment and underwent the same experiment with the exception of implantation of stellate ganglion electrodes and coronary cannulas.

OPEN-PERICARDIUM PREPARATION

The heart was approached through a left thoracotomy in the fourth intercostal space. The right stellate ganglion was removed with cautery through a retroesophageal approach. The central branches of the left
stellite ganglion and the sympathetic chain below the ganglion were cut; the cardiac branches were left intact. Blood loss was estimated (50–150 ml) and replaced with 6% dextran (75,000 molecular weight) in saline.

The pericardium was opened, and a metal cannula with a ring was placed in the coronary sinus via the right auricle and coronary sinus ostium with the ring holding the sinus open. The cannula was held in a fixed position by a suture that was passed around the coronary sinus and tied down in a groove in the cannula ring. This arrangement permitted continuous sampling of coronary sinus blood from a fixed site without obstruction of sinus flow or suction of the cannula against the vessel wall. The position of the cannula was determined post-mortem and was found to vary from 15 to 23 mm from the coronary ostium in the seven dogs.

CLOSED-CHEST PREPARATION

The dog was given a preanesthetic of Inovar-vet (McNeil Laboratories) (0.1 ml/kg, iv) and anesthetized with halothane. A left thoracotomy was performed under sterile conditions, and two stainless steel wire (Mediwire 316 SS-7/44) electrodes were placed encircling the left stellate ganglion, brought out through the chest wall, and left subcutaneous. A recovery period of 7-27 days was allowed.

The dog was then anesthetized with chloralose and prepared as described in the section entitled General Preparation. A no. 8 Sones catheter (U. S. Catheter & Instrument Co. model 5421) was inserted into the coronary sinus by use of a fluoroscope. The position of the catheter tip was determined post-mortem and was found to be between 20 and 48 mm from the coronary sinus ostium in the seven dogs.

A cannula-tip coronary blood flow transducer (14) was inserted via the right carotid artery, passed through the ascending aorta and the coronary ostium, and wedged in the circumflex coronary artery. Blood flowed from the aorta through the cannula into the coronary artery. The seal between the transducer tip and the coronary artery was verified by a 10-μg injection of nitroglycerin through a side injection tube (14). The left chest was opened with a small incision in the second intercostal space for stimulation of the left stellate ganglion.

The flow transducer was calibrated in situ post-mortem at the end of the experiment. The left chest and the pericardium were opened, the circumflex coronary artery was tied off proximal and distal to the flow transducer tip, the artery was incised, and a Silastic tube was fitted.

CLOSED-PERICARDIUM PREPARATION

The dog was anesthetized and prepared as described in the section entitled General Preparation. A Sones catheter was then inserted into the coronary sinus by use of a fluoroscope. The position of the catheter tip was determined post-mortem and was found to be between 20 and 48 mm from the coronary sinus ostium in the seven dogs.

Koberstein et al. (13) have demonstrated that coronary sinus blood may be withdrawn up to a rate of 30 ml/min without atrial contamination when the catheter tip is 15 mm or more inside the coronary sinus ostium.
OXYGEN TENSION MEASUREMENT

Blood oxygen tension was continuously measured with a specially designed cuvette (15). Flow rates in the coronary sinus catheter varied between 7.0 and 13.2 ml/min in the different dogs. The reported oxygen tension values are corrected 1% at these flow rates (15). Oxygen tension in the femoral artery was continuously measured from a T-cannula in the left femoral artery in the seven open-pericardium and the seven closed-chest dogs but not in the closed-pericardium group.

The transit delay from the sampling point to the electrode through the catheter and the pump tubing was timed for each catheter-flow combination with a stopwatch. For the coronary sinus measurement, it varied between 7.0 and 10.7 seconds in the different dogs; for the femoral artery, it varied between 5.8 and 9.8 seconds.

All reported oxygen tension values have had the appropriate transit time delay subtracted and are therefore equivalent to values that would have been obtained with the electrode placed in the coronary sinus or the femoral artery. The oxygen tension measurements shown as original records in Figures 1, 3, and 5 have also been corrected by a shift of the time axis by the appropriate amount.

The oxygen electrodes were calibrated with nitrogen and with an oxygen-nitrogen mixture (4% oxygen for the coronary sinus and 12% oxygen for the femoral artery) before and after each stimulation—approximately 5 minutes apart. The two calibrations had to agree within 1 mm Hg for the coronary sinus and within 2.5 mm Hg for the femoral artery or the data from that run were discarded.

EXPERIMENTAL DESIGN

The left stellate ganglion was stimulated at 15 Hz, 3 msec, and 4-7 v for 90 seconds in each part of a three-part experiment. Since each dog served as its own control, all dogs underwent all three parts of the experiment. (1) In the vagotomy control part of the experiment, the cervical vagus was cut bilaterally to prevent reflex vagal effects secondary to sympathetic stimulation. (2) In the beta-receptor blockade part, the effect of increased cardiac oxygen metabolism was distinguished from direct coronary vasoconstriction, since beta-receptor blockade blunts the positive chronotropic and inotropic effects of sympathetic stimulation and thus obducts the increase in cardiac oxygen metabolism (7, 10). (3) In the alpha- and beta-receptor blockade part of the experiment, alpha-receptor blockade was induced together with the beta-receptor blockade that remained from part 2, since part 3 followed part 2 within 40 minutes. If the decrease in coronary sinus oxygen tension observed in part 2 was due to coronary artery vasoconstriction, then the response should have been blocked by an alpha-receptor blocking agent.

DRUGS

Propranolol (Ayerst Laboratories) was diluted with isotonic saline to a concentration of 2 mg/ml for intravenous administration. A large dose (2.0 mg/kg) of propranolol was administered in part 2 of the experiment without supplementation in part 3. The effectiveness of beta-receptor blockade was demonstrated by the absence of tachycardia during sympathetic stimulation.

FIGURE 2
Average response during stimulation of the left stellate ganglion under vagotomy control conditions. The dashes indicate ± 1 SE. The number of dogs is indicated in each section. P<sub>1</sub> = oxygen tension.
Beta receptors were blocked with propranolol (2.0 mg/kg, iv), and sympathetic coronary vasoconstriction was unmasked. Despite the beta-receptor blockade of the chronotropic and inotropic effects of sympathetic stimulation, coronary sinus oxygen tension (P02) decreased. This finding implies that alpha-receptor coronary vasoconstriction was the responsible mechanism.

Dibozane (1, 4-[(bis-1, 4-benzodioxan-2-yl methyl)piperazine] (McNeil Laboratories), an alpha-receptor blocking agent, was diluted with 1% phosphoric acid in isotonic saline to a concentration of 3 mg/ml for intravenous administration.

DATA ANALYSIS

Analog records were read every 15 seconds before and after sympathetic stimulation and every 5 seconds during the stimulation. At each time point mean arterial blood pressure, mean coronary blood flow, heart rate, and arterial and coronary sinus oxygen tension were read. A straight line was drawn through the diastolic portion of the pulsatile flow record after systole and before the atrial cove. This part of the tracing is after the incisura vibrations on the aortic blood pressure record and is characteristically the most orderly portion of the flow record during diastole. Simultaneous measurements of flow and aortic blood pressure were made during the cardiac cycle. Diastolic coronary artery resistance (pressure/flow) was calculated assuming atmospheric pressure for the venous pressure. The data were entered on punched cards for computer analysis by Biomedical Computer Program 01D (16). Diastolic coronary artery resistance is expressed in terms of the prestimulation value, and this value for an individual dog was taken as the average of the values 60, 45, 30, and 15 seconds before stimulation. The percent of the prestimulation value was calculated for each time point (+60 seconds through +160 seconds) for each dog and each experimental condition. The averages of these values are shown in the figures.

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The standard error given in the figures is a measure of the variability among dogs and is based on the statistically independent responses of the dogs (degrees of freedom equal n - 1). Two-tailed, one-sample, paired t-tests were used to test the statistical significance of the observed difference between parts 2 and 3 for each time point for each dog. The responses from the three different preparations were analyzed separately, and then with all three groups combined. The effects of stimulation were similar in all three groups, and the conclusions were the same in all preparations.

Results

Under control conditions with both vagi cut, stimulation of the left stellate ganglion increased mean blood pressure 46 mm Hg and heart rate 63 beats/min. Average oxygen tension in the coronary sinus fell 4 mm Hg with sympathetic stimulation; mean blood flow in the circumflex coronary artery increased 38 ml/min, and diastolic coronary resistance decreased to 58% of the prestimulation value (Figs. 1 and 2).

After beta-receptor blockade with propranolol, stimulation of the stellate ganglion no longer resulted in tachycardia, and mean blood pressure increased 16 mm Hg. However, average oxygen tension in the coronary sinus decreased 6 mm Hg during sympathetic stimulation. Mean circumflex
coronary artery blood flow decreased 9 ml/min, at the onset of stimulation, returned to prestimulation values, and increased 12 ml/min after the cessation of the stimulation. Diastolic coronary resistance rose to 210% of the prestimulation value 5 seconds after the onset of stimulation, returned to approximately 122% of the prestimulation value during the 90-second stimulation, and decreased to 88% of the prestimulation value 10 seconds after cessation of the stimulation (Figs. 3 and 4).

After alpha-receptor blockade was added, stimulation of the stellate ganglion failed to elicit tachycardia, indicating that beta-receptor blockade remained from part 2. Mean blood pressure increased 9 mm Hg. Most importantly, coronary sinus oxygen tension no longer decreased, and mean coronary blood flow as well as the diastolic coronary resistance was nearly constant. A small, brief increase in coronary blood flow accompanied by a brief elevation in coronary sinus oxygen tension was observed in the initial 10–15 seconds of the stimulation (Figs. 5 and 6).

The critical comparison in this investigation is between the average measurements of coronary sinus oxygen tension and diastolic coronary resistance in parts 2 and 3 (Fig. 7). It can be seen in Figure 7 that sympathetic stimulation resulted in a prompt and sustained fall in coronary sinus oxygen tension; a sustained increase in diastolic coronary resistance occurred with beta-receptor blockade in part 2 but did not occur in part 3 when alpha-receptor blockade was added. The differences before and after alpha-receptor blockade were significant, as indicated by the P values shown in Figure 7. Thus, the decrease in coronary sinus oxygen tension after beta-receptor blockade was due to alpha-receptor vasoconstriction.

Discussion

In a previous study, we have demonstrated alpha-receptor coronary vasoconstriction after it has been unmasked by beta-receptor blockade under comparable conditions (4). Ross and Mulder (6) have also observed direct sympathetic coronary vasoconstriction after an infusion of propranolol. Ek and Åblad (7), McRaven et al. (8), Mark et al. (9), and Nayler and Carson (10) have reported that sympathetic alpha-receptor coronary vasoconstriction may be unmasked with several beta-receptor blocking agents, including practolol.

Shipley and Gregg (17) demonstrated in 1945 that coronary venous oxygen levels decrease with stimulation of the stellate ganglion. This effect has been confirmed by Juhász-Nagy and Szentiványi (18), Berne et al. (2), Brown (19), Ek and Åblad (7), and Obeid et al. (20). The results in part 1 further confirm that sympathetic stimulation results in decreased coronary venous oxygen tension. Shipley and Gregg (17), Granata et al. (3), Obeid et al. (20), Ek and Åblad (7), and Nayler and

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Alpha-receptor blockade with Dibozane (3.0 mg/kg, iv) has been added to the previous beta-receptor blockade. Stimulation of the stellate ganglion no longer resulted in coronary vasoconstriction and coronary sinus oxygen tension (PO$_2$) did not decrease.

Carson (10) have all demonstrated increased cardiac oxygen metabolism with stimulation of the stellate ganglion under control conditions. Ek and Åblad (7) and Nayler and Carson (10) have shown that the increase in oxygen metabolism produced by sympathetic stimulation is blunted by beta-receptor blockade.

The major assumption in this experiment was that coronary sinus blood oxygen tension reflects myocardial oxygen tension. Myocardial and coronary sinus oxygen tensions are probably not equal; however, it is reasonable to assume that a fall in coronary sinus oxygen tension reflects a decrease in myocardial oxygen tension. Direct measurement of myocardial oxygen tension is technically difficult and would give a value for only a small area of the myocardium. Measurement in the coronary sinus has the advantages that a larger area of cardiac muscle is represented and the myocardium is not penetrated.

The decrease in coronary sinus oxygen tension observed under control conditions in part 1 may have been due to either a relative coronary vasoconstriction or an increase in myocardial oxygen metabolism, or both. A change in coronary sinus oxygen tension is interpreted as prima facie evidence of an alteration of the balance between blood flow and oxygen metabolism. Clearly, coronary blood flow did not increase in proportion to the increase in metabolism.

The fall in coronary oxygen tension in part 2 is interpreted to result from alpha-receptor sympathetic coronary vasoconstriction unmasked by beta-receptor blockade. The initial decrease in coronary blood flow resulted in an increase in oxygen extraction that was maintained throughout the 90-second stimulation by the sustained increase in coronary vascular resistance despite an increase in aortic blood pressure. The augmented flow at the end of the stimulation (off response) returned coronary sinus oxygen tension to prestimulation values. These findings indicate that alpha-receptor sympathetic coronary vasoconstriction results in increased oxygen extraction and decreased coronary sinus oxygen tension. Assuming that a decrease in coronary sinus oxygen tension indicates a fall in myocardial oxygen tension, the results suggest that myocardial oxygen tension may be regulated by sympathetic vasomotion as well as by myocardial oxygen metabolism and local vascular control mechanisms.

The coronary vasoconstriction was subsequently blocked in part 3 by alpha-receptor blockade, and coronary sinus oxygen tension no longer decreased...
with sympathetic stimulation. These experiments test the hypothesis that the fall in coronary sinus oxygen tension observed following propranolol administration (part 2) is due to sympathetic alpha-receptor vasoconstriction (Fig. 7). These experiments do not indicate whether limited vasodilation (relative coronary vasoconstriction) is an important mechanism in lowering coronary venous oxygen tension during sympathetic stimulation without beta-receptor blockade (part 1). Propranolol probably does not interfere with the local metabolic vasodilator mechanism of the heart. Thus, it is plausible that the alpha-receptor vasoconstriction demonstrated in part 2 may have also played a role in lowering coronary sinus oxygen tension before beta-receptor blockade in part 1.

The transient small increase in coronary blood flow and the accompanying increase in coronary sinus oxygen tension at the beginning of stimulation after combined alpha- and beta-receptor blockade remain unexplained. Atropine (0.5 mg/kg, iv) had no effect on this transient vasodilation in two dogs.

In conclusion, continuous measurement of coronary sinus oxygen tension in this investigation demonstrated that sympathetic alpha-receptor...
coronary vasoconstriction is capable of lowering myocardial oxygen tension. This finding indicates that blood flow to the heart like that to other vascular beds is potentially under autonomic as well as metabolic control.

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References


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