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Hypoxia-induced vasodilation in the right coronary circulation of conscious dogs: Role of adrenergic activation

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Abstract

The role of adrenergic activation in the right coronary (RC) flow response to hypoxia has not been previously delineated, and limited information from left coronary studies is inconsistent. Seven dogs were instrumented with catheters implanted in the aorta and in the right ventricle to measure aortic pressure and right ventricular (RV) pressure, respectively. A flow transducer was placed around the RC artery to measure RC flow. After recovery from surgery, the dogs were exposed to systemic hypoxia in a Plexiglas chamber ventilated with N₂. Percent O₂ in the chamber was monitored, and blood samples and hemodynamic data were collected as chamber O₂ was progressively reduced to ~6%. The chamber was then opened, and the dog breathed room air. Phentolamine, 1 mg/kg, and propranolol, 2 mg/kg, were then administered via the RV catheter to achieve adrenergic blockade, and the hypoxia protocol was repeated. During hypoxia, arterial PO₂ progressively fell from 87 ± 3 to 25 ± 1 mmHg during untreated control condition and from 90 ± 4 to 23 ± 1 mmHg during adrenergic blockade. In the unblocked condition, hypoxia caused increases in aortic pressure, heart rate, RV pressure, and RV dP/dt_{max}. After adrenergic blockade, normoxic aortic pressure was reduced; heart rate and RV dP/dt_{max} tended to be lower. Aortic pressure rose during hypoxia, but to lesser values than before blockade. Heart rate and RV dP/dt_{max} also increased, but only at more severe hypoxia, and these values were less than before blockade. Normoxic flow and hypoxia-induced increases in RC flow and conductance were not altered by blockade. The relationship between RC conductance and RV triple product, an index of RV O₂ demand, was steeper after blockade. These findings indicate that in the normal, unblocked condition, RC flow during hypoxia is restrained by an adrenergic-mediated increase in RC vasomotor tone.

Introduction

Systemic hypoxia activates reflexes that increase myocardial O₂ consumption by increasing myocardial contractility, heart rate and systemic blood pressure largely resulting from activation of the sympathetic nervous system (Doherty and Liang, 1984; Downing and Siegel, 1963; Erickson and Stone, 1972; Hammill et al., 1979; Hoka et al., 1989; Horwitz et al., 1969; Martinez et al., 2005). Catecholamines released by the adrenal medulla and norepinephrine released from sympathetic nerve terminals activates both α and β adrenoceptors (Bevan, 1978). α -adrenoceptor activation of vascular smooth muscle causes vasoconstriction of peripheral and coronary vessels (Berne and Rubio, 1978; Bevan, 1978; Feigl, 1983; Heusch

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et al., 1984; Mohrman and Feigl, 1977; Zong et al., 2004). However, activation of myocardial β_1 - and β_2 - adrenoceptors increases heart rate and myocardial contractility, which result in release of vasodilatory metabolites (Berne and Rubio, 1978; Feigl, 1983). Cardiodepressive β_3 - adrenoceptors are also present on cardiac myocytes (Kitamura, et al., 2000), but their effect is normally overwhelmed by the positive inotropic action of β_1 - and β_2 -adrenoceptors. In addition, activation of β_1 - and β_2 -adrenoceptors causes coronary vasodilation (Feigl, 1998; Gorman et al., 2000; Miyashiro and Feigl, 1993). These direct and indirect vasodilatory mechanisms compete effectively with α -adrenoceptor-mediated coronary vasoconstriction, and the net coronary response to cardiac sympathetic nerve stimulation is vasodilation (Mohrman and Feigl, 1977; Mudge et al., 1979). If hypoxia is not too severe, coronary vasodilation enables myocardial O₂ delivery to balance increased myocardial O₂ demand in spite of reduced arterial O₂ content (Herrmann and Feigl, 1992; Martinez et al., 2005).

The role of sympathetic activation in controlling coronary blood flow during hypoxia is complex, since sympathetic activation directly initiates both vasodilatory and vasoconstrictory mechanisms and indirectly initiates vasodilatory mechanisms. Doherty and Liang (1984) reported that canine left coronary blood flow of conscious dogs increased by ~100 ml/min/100 g during inspiration of 8% O₂ and by ~540 ml/min/100 g during inspiration of 5% O₂. α - plus β_1 - and β_2 -adrenergic blockade (hereafter referred to as “adrenergic blockade” with the understanding that β_3 -adrenoceptors are resistant to propranolol) caused no significant effect on the flow increase observed at 8% O₂ inspiration, however, this adrenergic blockade reduced the hyperemic response to 5% O₂ to ~300 ml/min/100 g. Herrmann and Feigl (1992) reported an increase in left coronary flow of ~160 ml/min/100 g in anesthetized dogs breathing 7–10% O₂. Although Doherty and Liang observed no effect of adrenergic blockade in dogs respiring 8% O₂, Herrmann and Feigl found that adrenergic blockade markedly reduced the hyperemic response from ~160 ml/min/100 g to ~44 ml/min/100 g. Interpretation of the results of these earlier studies is confounded by unspecified reductions in myocardial O₂ demand caused by adrenergic blockade.

No studies have reported the effects of adrenergic blockade on hypoxia-induced RC hyperemia. Considering previously described differences in mechanisms of O₂ balance between the left and right ventricles (Hart et al., 2001; Zong et al., 2005), and the differences in reported effects of adrenergic blockade on left coronary hypoxia-induced hyperemia, this study was conducted in conscious, instrumented dogs to define the role of sympathetic activation in determining RC blood flow during graded, systemic hypoxia. We found that adrenergic blockade failed to attenuate hypoxia-mediated increases in RC blood flow over a wide range of inspired O₂. In fact, after adrenergic blockade, RC vasodilation was more sensitive to hypoxia-induced increases in right ventricular (RV) mechanical function, consistent with an α -adrenergic-mediated constraint of RC hyperemia during hypoxia in the normal, unblocked condition.

Materials and Methods

Animal instrumentation

This investigation was approved by the Institutional Animal Care and Use Committee and was conducted in accordance with the *Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health (NIH Publication No. 85-23, Revised 1996). Experiments were performed on seven adult mongrel dogs (21–28 kg) of either sex.

Thirty minutes after preanesthesia treatment with Acepromazine (0.15 mg/kg sc), anesthesia was induced by thiopental sodium (5 mg/kg iv) and maintained by mechanical ventilation with isoflurane gas (1–3%) after endotracheal intubation. Under sterile conditions, a thoracotomy was performed in the fourth right intercostal space. A 17-gauge pressure monitoring catheter (LAP 17, Edwards Lifesciences) was implanted into the ascending aorta to measure aortic

blood pressure and to obtain arterial blood samples. A nonbranching section of the RC artery was dissected free for 1–2 cm to affix a 2-mm diameter flow transducer (Transonic Systems, Inc.). A coextruded polyurethane catheter (Putnam Plastics) was implanted into the lumen of the right ventricle through a stab incision.

At the conclusion of the instrumentation, catheters and the flow transducer cable were brought out of the thorax through the third and fifth right intercostal spaces, tunneled under the skin, and exteriorized between the shoulders through individual puncture wounds. The chest was closed, and the pneumothorax evacuated through a chest tube. An antibiotic (Clavamox, 13.75 mg/kg, twice daily, po) and aspirin (162–300 mg po) were given for 10 days after surgery. After bandaging, the animal was fitted with a jacket (Alice King Chatham) to protect the catheters.

Experimental protocol and data collection

When the animals had recovered from the surgical procedures (10–12 days after surgery), measurements were obtained with the animal standing quietly in a sling in a Plexiglas chamber. RC flow was measured with a Transonic Systems, Inc., T206 series flowmeter. An external pressure transducer (Hewlett-Packard model 1290C) was positioned at mid-heart level and connected to the aortic catheter to measure systemic arterial pressure. A 3F high-fidelity Mikro-tip catheter pressure transducer (Millar Instruments) was introduced into the polyurethane RV catheter through a Tuohy-Borst hemostatic control valve (Mallinckrodt Medical), to measure RV pressure and also to infuse phentolamine and propranolol at the time of experiment while maintaining a fluid tight seal around the Millar catheter. Aortic pressure, RC blood flow and RV pressure were recorded on a multichannel Hewlett-Packard chart recorder and an EMKA Technologies data acquisition system. This data acquisition system computed real time values for right ventricular $dP/dt_{\max}$, an index of systolic myocardial contractility and right ventricular $dP/dt_{\min}$, an index of diastolic myocardial compliance.

Arterial blood samples were collected anaerobically and chilled on ice until analysis. O_2 content was measured with an Instrumentation Laboratory model 682 Co-Oximeter, and PO_2 was measured with an Instrumentation Laboratory Synthesis 30 blood gas analyzer. Plasma glucose and lactate concentrations were measured with a Radiometer model EML 105 analyzer.

After normoxic data were collected, the chamber was closed and nitrogen was introduced progressively to reduce the O_2 concentration within the Plexiglas chamber. The percent O_2 within the chamber was monitored with an O_2 analyzer (Alpha Omega Instrument-Series 2000). When RC blood flow reached a steady state (3–5 min) at different degrees of hypoxia (from 20–6% O_2), arterial blood samples were collected and other hemodynamic data were recorded. After the blood samples were collected at the most severe hypoxia, the chamber was opened and the dogs were allowed to breathe room air. Phentolamine (1 mg/kg, iv, Gwirtz and Stone, 1981; Gorman et al., 2000), a non-specific α -adrenoceptor blocker, and dl-propranolol (2 mg/kg, iv, Herrmann and Feigl, 1992), a β_1 - and β_2 -adrenoceptor blocker, were then administered through the RV catheter into the right ventricle. Fifteen minutes after adrenergic blockade, normoxic values were again obtained, and then the hypoxia protocol was repeated. Arterial blood samples and hemodynamic data were collected at degrees of hypoxia similar to those of the unblocked condition.

After completion of the protocols, the animals were anesthetized with pentobarbital sodium (30 mg/kg, via RV catheter) and then euthanized by injecting saturated KCl solution sufficient to cause ventricular fibrillation. After the chest was opened, a catheter was inserted into the RC ostium, and 15 ml of 2.5 % Evans Blue dye was injected to delineate the RC perfused territory. This dyed tissue was then carefully excised and weighed, so that RC blood flow could be expressed per 100 gram of tissue.

Statistical analyses

All values are expressed as means $\pm$ SE. Results were analyzed with two factor (factor A, adrenergic blockade; factor B, hypoxia), repeated measures analysis of variance (ANOVA) to detect effects of 1) blockade and 2) hypoxia. When significance ($P < 0.05$) was detected by ANOVA, a Student-Newman-Keuls multiple comparison test was performed. Linear regression analysis was used to define relationships between right coronary conductance and triple product. Analysis of covariance was used to compare these relationships. Statistical procedures were performed with GB-Stat statistical software, version 9.0.

Results

Effects of graded hypoxia during the untreated condition

Blood gas data are presented in Table 1. Graded hypoxia caused stepwise decreases in arterial PO_2 from 87 ± 3 mmHg (normoxia) to 71 ± 2 mmHg (mild hypoxia), to 46 ± 1 mmHg (moderate hypoxia), and to 25 ± 1 mmHg (severe hypoxia). Arterial O_2 content fell to 7.1 ± 0.1 ml O_2 /100 ml blood during severe hypoxia. Although small hypoxia-induced increases in hematocrit and hemoglobin were not significant for this unblocked condition, an overall significant effect of hypoxia on these variables was detected by the factorial ANOVA. Arterial PCO_2 was significantly decreased and arterial pH was increased at the most severe hypoxia. Arterial glucose was unaffected by hypoxia, but arterial lactate increased at severe hypoxia.

Hemodynamic data are presented in Table 2. In the untreated condition, mean aortic pressure, heart rate, and $RV\ dp/dt_{max}$ increased during hypoxia. $RV\ dp/dt_{min}$ was unaffected by hypoxia in the untreated condition or after adrenergic blockade. RC blood flow for normoxic and hypoxic conditions is illustrated in Figure 1. RC blood flow was 63 ± 5 ml/min/100 g at normoxia and increased by 57 % at moderate hypoxia and increased by 198 % at severe hypoxia. To account for hypoxia-induced changes in the mean aortic pressure, RC conductance was computed (RC blood flow / mean aortic pressure) and is illustrated in Figure 2. RC conductance was 0.54 ± 0.05 ml/min/100 g/mmHg during normoxia and increased by 133 % at severe hypoxia. Although arterial O_2 content fell during hypoxia, RC O_2 delivery to RV myocardium increased by 18 % at moderate hypoxia and by 25 % at severe hypoxia (Table 1).

Effects of Adrenergic Blockade

Graded hypoxia again caused stepwise decreases in arterial PO_2 and PCO_2 which, for each degree of hypoxia, were similar to values observed before blockade (Table 1). Hemoglobin, hematocrit, arterial O_2 content, and RC O_2 delivery were significantly reduced after adrenergic blockade (Table 1). In the normoxic condition, adrenergic blockade caused a significant fall in mean aortic pressure, and tended to reduce heart rate and $RV\ dp/dt_{max}$ (Table 2). Considering all conditions, adrenergic blockade caused significant decreases in mean aortic pressure and $RV\ dp/dt_{max}$, and tended to reduce heart rate. RV pressure, $RV\ dp/dt_{min}$, and RC flow were unaffected by adrenergic blockade in either the normoxic condition, or when all conditions were considered (Table 2 and Figure 1). RC conductance values after blockade were essentially identical to those in the untreated condition (Figure 2).

Effects of graded hypoxia after adrenergic blockade

Hypoxia following adrenergic blockade caused increases in heart rate, dP/dt_{max} , RC flow, and RC conductance (Table 2). Mean aortic pressure and RV pressure were increased at the most severe hypoxia. Figure 1 demonstrates the marked capacity for RC flow to increase during hypoxia, and shows the similarity of RC flows before and after adrenergic blockade. Figure 2 shows that adrenergic blockade had no significant effect on RC conductance during normoxia and during graded hypoxia.

Hypoxia increased heart rate and RV $dP/dt_{\max}$, and tended to increase RV pressure (Table 2), whereas adrenergic blockade reduced RV $dP/dt_{\max}$ and tended to reduce heart rate. These changes in mechanical function would have affected RV myocardial O_2 demand. Since O_2 demand is a major determinant of coronary blood flow (Tune et al., 2004), it is important to examine RC vascular responses as a function of RV O_2 demand. In a previous investigation (Setty et al., 2002), we demonstrated a tight, linear relationship between RV O_2 consumption and the product of Heart Rate X RV Pressure X RV $dP/dt_{\max}$. This “triple product” was, thus, used as an index of myocardial RV O_2 demand in the present investigation, since for the aerobic myocardium, O_2 consumption reflects O_2 demand. In Figure 3, RC conductance is plotted as a function of this triple product. Regression analysis demonstrated linear relationships between conductance and triple product for both the untreated condition and after adrenergic blockade. Figure 3 shows that adrenergic blockade displaced the relationship between RC conductance and the index of RV O_2 demand upward and to the left. Thus, for the same degree of RV O_2 demand, RV conductance was greater and increased more steeply after adrenergic blockade. These data are consistent with the adrenergic restraint of hypoxia-mediated RC vasodilation in the normal, unblocked state.

Discussion

Hypoxia is a powerful stimulus to increase coronary blood flow. As O_2 partial pressure and content of the arterial blood decrease, metabolic signals produce coronary arteriolar relaxation to sustain O_2 delivery. At the same time, cardiac mechanical function increases, further increasing the metabolic signal to increase flow. Changes in cardiac mechanical function are largely in response to hypoxia-induced activation of the sympathetic nervous system, which influences coronary conductance as well as cardiac mechanical function. While the vasoconstrictory effects of coronary α -adrenoceptor activation and the vasodilatory effects of coronary β -adrenoceptor activation have been studied in a number of conditions, the role of adrenergic regulation of coronary blood flow during hypoxia is poorly understood. Two studies (Doherty and Liang, 1984; Hermann and Feigl, 1992) have addressed this issue with regard to the left coronary circulation with somewhat disparate results. No studies have reported on the role of the sympathetic nervous system in regulating RC blood flow during hypoxia.

Doherty and Liang (1984) investigated the effects of hypoxia and blockade of the sympathetic nervous system on left coronary flow and ventricular function of conscious dogs. Inspiration of 8% O_2 caused left coronary flow to increase by ~ 100 ml/min/100 g. Adrenergic blockade had no effect on this hyperemia, although left ventricular work was significantly reduced after blockade. Our findings in right ventricle agree with these observations, since adrenergic blockade reduced triple product (Figure 3), but had no effect on hypoxia-induced increases in RC flow or conductance (Figure 1 and Figure 2).

Hermann and Feigl (1992) conducted a related study in anesthetized dogs inspiring 7–10% O_2 . Before adrenergic blockade, hypoxia caused marked left coronary hyperemia. Adrenergic blockade then markedly blunted hypoxia-induced hypertension, tachycardia, myocardial oxygen consumption, and coronary hyperemia. Hermann and Feigl concluded that “much of the coronary vasodilation associated with systemic hypoxia is dependent upon adrenergic activation.” This conclusion, based on findings in an anesthetized model, conflicts with the earlier reported left coronary findings in conscious dogs of Doherty and Liang, 1984, where adrenergic blockage did not blunt the hyperemia caused by 8% O_2 , and with our current finding of pronounced hypoxia-induced RC hyperemia that was not blunted by adrenergic blockade (Figure 1).

Absence of a decrease in coronary flow after adrenergic blockade might suggest that, during hypoxia, left coronary vasodilation is driven primarily by decreased myocardial PO_2 ,

independent of changes in myocardial mechanical function. This explanation seems unlikely, since coronary flow is generally understood to be tightly coupled to myocardial function (Feigl, 1983). Another explanation might be that in the unblocked state, coronary vasodilation is restrained by α -adrenoceptor coronary constriction, which competes with vasodilatory mechanisms activated by β_1 - and β_2 -adrenoceptor mediated increases in myocardial O_2 demand and more directly by β_1 - and β_2 -mediated coronary vasodilation. Evidence of α -adrenoceptor left coronary flow restraint during hypoxia was demonstrated in the study of Doherty and Liang, where α -adrenoceptor blockade caused an increase in coronary flow while myocardial function fell. However, removal of this restraint by adrenergic blockade might be balanced by the loss of direct and indirect β -adrenoceptor-mediated vasodilation, resulting in little change in coronary flow as observed by Hermann and Feigl. Thus, different results from experiments in conscious dogs (Doherty and Liang and the current investigation) and in anesthetized dogs might be explained if in anesthetized dogs there is lesser α -mediated coronary vasoconstriction or greater β -mediated vasodilation than occurs in the conscious state. Considering that Hermann and Feigl's observations were made in the anesthetized state, we speculate that the former is the most likely explanation.

When the dogs of Doherty and Liang's study inspired 5% O_2 , increases in cardiac work and coronary flow were much greater than were observed during inspiration of 8% O_2 , as we observed in the current study during severe hypoxia. However, we found that adrenergic blockade did not blunt hypoxic hyperemia during this condition, whereas Doherty and Liang reported a large decrease in left coronary hyperemia. In both studies, cardiac function was reduced after blockade. The decrease in function is consistent with blockade of the normal, hypoxia-induced, sympathetic-mediated enhancement of myocardial contractility (Doherty and Liang, 1984; Downing and Siegel, 1963; Erickson and Stone, 1972; Hammill et al., 1979; Hoka et al., 1989; Horwitz et al., 1969; Martinez et al., 2005), but the possibility that unblocked β_3 -adrenoceptors contributed to this depressed function (Kitamura et al, 2000) must be acknowledged. In any case, absence of a decline in RC flow after adrenergic blockade would be consistent with significant α -adrenergic-mediated vasoconstriction in the unblocked state.

When RC conductance was examined as a function of the triple product, an index of RV myocardial O_2 demand and consumption (Figure 3), further evidence of adrenergic constraint of RC flow was apparent. With adrenergic blockade, the slope of this relationship was significantly steeper compared to the untreated group. These results indicate that adrenergic stimulation normally restrains hypoxia-induced RC hyperemia. Since coronary flow fell along with left ventricular work after adrenergic blockade in the study of Doherty and Liang (Doherty and Liang, 1984), but was sustained in the current study, we conclude that adrenergic restraint of coronary flow during hypoxia is more potent in the RC circulation.

We have previously demonstrated that α -adrenergic activation restrains canine RC blood flow during treadmill exercise and that α -adrenergic vasoconstriction is more potent in RC than left coronary circulation (Zong et al., 2004). This restraint forces the RV to utilize the relatively large RC O_2 extraction reserve, so that increased RV O_2 demand could be met without increased RC conductance during mild exercise (Hart et al., 2001). In the current investigation, RC venous blood was not collected, so data for RV O_2 extraction are not available. However, the small, insignificant changes in RC flow and conductance despite a 26 mmHg fall in arterial PO_2 during mild hypoxia appear consistent with the findings in mild exercise. It should be noted that RC O_2 delivery to the right ventricle actually increased during moderate and severe hypoxia, both before and after adrenergic blockade (Table 1). This demonstrates the ability of hypoxia to activate metabolic vasodilatory mechanisms sufficient to sustain and even increase RV O_2 supply, either in the presence or absence of adrenergic mechanisms.

After adrenergic blockade, RC O₂ delivery was impacted by a small, but significant, decrease in arterial O₂ content, secondary to reduced hematocrit, as reported by others (Longhurst et al. 1986). The cause of this decreased hematocrit is uncertain, but may reflect increased splenic uptake of erythrocytes after blockade.

It should be noted that in this report, as in earlier relevant investigations, adrenergic blockade refers to α - plus β_1 - and β_2 -adrenergic blockade. Thus, any effects of unblocked β_3 -adrenoceptors would have been unmasked, as would effects of non-adrenergic sympathetic neurotransmitters. However, at present the function and importance of these mechanisms in cardiac and coronary physiology is poorly understood. It should also be noted that conclusions based on comparisons of results between various studies of adrenergic blockade will be affected by the effectiveness of the blockade in the respective studies. In this regard, doses of blocking drugs administered in the current study were the same as or greater than the doses administered in the relevant left coronary studies (Doherty and Liang, 1984; Hermann and Feigl, 1992). Although densities of adrenoceptor densities in atrial and ventricular tissue have been described (Brodde et al, 2001), adrenoceptor densities of right and left canine ventricular myocardium and left and right canine coronary circulations have not been reported. However, it seems reasonable that the adrenergic blocking drugs employed in this investigation would have been equally effective in left and right myocardium and in left and right coronary vasculature.

In summary, this investigation in instrumented, conscious dogs found that adrenergic blockade did not reduce RC blood flow or conductance during graded hypoxia, although RV mechanical function was reduced. Similar RC flows after blockade despite lesser RV O₂ demand indicates that RC flow is normally restrained by an adrenergic mechanism during hypoxia. Thus, RC α -adrenergic vasoconstriction appears to predominate over RC β -adrenergic vasodilation during graded systemic hypoxia. Additionally, this α -adrenergic restraint appears to be more potent in the RC than in the left coronary circulation.

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References

- Berne, RM.; Rubio, R. Coronary circulation. In: Berne, RM.; Serelakis, N., editors. Handbook of physiology section 2, The cardiovascular system, volume I, The heart. Bethesda, MD: American Physiology Society; 1978. p. 873-952.
- Bevan JA. Response of blood vessels to sympathetic nerve stimulation. *Blood Vessels* 1978;15:17–25. [PubMed: 204380]
- Brodde O-E, Bruck H, Leineweber K, Seyfarth T. Presence, distribution and physiological function of adrenergic and muscarinic receptor subtypes in the human heart. *Basic Res. Cardiol* 2001;96:528–538. [PubMed: 11770070]
- Doherty JU, Liang C. Arterial hypoxemia in awake dogs. Role of the sympathetic nervous system in mediating the systemic hemodynamic and regional blood flow responses. *J. Lab. Clin. Med* 1984;104:665–677. [PubMed: 6149249]
- Downing SE, Siegel JH. Baroreceptor and chemoreceptor influences on sympathetic discharge to the heart. *Am. J. Physiol* 1963;204:471–479.
- Erickson HH, Stone HL. Cardiac beta-adrenergic receptors and coronary hemodynamics in the conscious dog during hypoxic hypoxia. *Aerosp. Med* 1972;43:422–428. [PubMed: 4402980]
- Feigl EO. Coronary physiology. *Physiol Rev* 1983;63:1–205. [PubMed: 6296890]
- Feigl EO. Neural control of coronary blood flow. *J. Vasc. Res* 1998;35:85–92. [PubMed: 9588871]
- Gorman MW, Tune JD, Richmond KN, Feigl EO. Feedforward sympathetic coronary vasodilation in exercising dogs. *J. Appl. Physiol* 2000;89:1892–1902. [PubMed: 11053341]

- Gwartz PA, Stone HL. Coronary blood flow and myocardial oxygen consumption after α -adrenergic blockade during submaximal exercise. *J. Pharmacol. Exp. Ther* 1981;217:92–98. [PubMed: 6110777]
- Hammill SC, Wagner WW, Latham LP, Frost WW, Weil JV. Autonomic cardiovascular control during hypoxia in the dog. *Circ. Res* 1979;44:569–575. [PubMed: 428052]
- Hart BJ, Bian X, Setty S, Gwartz PA, Downey HF. Right ventricular oxygen supply/demand balance in the exercising dog. *Am. J. Physiol. Heart. Circ. Physiol* 2001;281:H823–H830. [PubMed: 11454587]
- Hermann SC, Feigl EO. Adrenergic blockade blunts adenosine concentration and coronary vasodilation during hypoxia. *Circ. Res* 1992;70:1203–1216. [PubMed: 1315635]
- Heusch G, Deussen A, Schipke J, Thamer V. α_1 - and α_2 -adrenoceptor-mediated vasoconstriction of large and small canine coronary arteries in vivo. *J. Cardiovasc. Pharmacol* 1984;6:961–968. [PubMed: 6209507]
- Hoka S, Bosnjak ZJ, Arimura H, Kampine JP. Regional venous outflow, blood volume, and sympathetic nerve activity during severe hypoxia. *Am. J. Physiol* 1989;256:H162–H170. [PubMed: 2912179]
- Horwitz LD, Bishop VS, Stone HL, Stegall HF. Cardiovascular effects of low-oxygen atmospheres in conscious and anesthetized dogs. *J. Appl. Physiol* 1969;27:370–373. [PubMed: 5804135]
- Kitamura T, Onishi K, Dohi K, Okinaka T, Isaka N, Nakano T. The negative inotropic effect of beta3-adrenoceptor stimulation in the beating guinea pig heart. *J. Cardiovasc. Pharmacol* 2000;35:786–790. [PubMed: 10813382]
- Longhurst JC, Musch TI, Ordway GA. O_2 consumption during exercise in dogs-roles of splenic contraction and α -adrenergic vasoconstriction. *Am. J. Physiol. Heart. Circ. Physiol* 1986;251:H502–H509.
- Martinez RR, Setty S, Zong P, Tune JD, Downey HF. Nitric oxide contributes to RC vasodilation during systemic hypoxia. *Am. J. Physiol. Heart. Circ. Physiol* 2005;288:H1139–H1146. [PubMed: 15513958]
- Miyashiro JK, Feigl EO. Feedforward control of coronary blood flow via coronary beta-receptor stimulation. *Circ. Res* 1993;73:252–263. [PubMed: 8392446]
- Mohrman DE, Feigl EO. Competition between sympathetic vasoconstriction and metabolic vasodilation in the canine coronary circulation. *Circ. Res* 1977;42:79–86. [PubMed: 201392]
- Mudge GH Jr, Goldberg S, Gunthier S, Mann T, Grossman W. Comparison of metabolic and vasoconstrictor stimuli on coronary vascular resistance in man. *Circulation* 1979;59:544–550. [PubMed: 761335]
- Setty S, Tune JD, Downey HF. Nitric oxide modulates right ventricular flow and oxygen consumption during norepinephrine infusion. *Am. J. Physiol. Heart. Circ. Physiol* 2002;282:H696–H703. [PubMed: 11788420]
- Tune JD, Gorman MW, Feigl EO. Matching coronary blood flow to myocardial oxygen consumption. *J. Appl. Physiol* 2004;97:404–441. [PubMed: 15220323]
- Zong P, Sun W, Setty S, Tune JD, Downey HF. Alpha-adrenergic vasoconstrictor tone limits right coronary blood flow in exercising dogs. *Exp. Biol. Med* 2004;229:312–322.
- Zong P, Tune JD, Downey HF. Mechanisms of oxygen demand/supply balance in the right ventricle. *Exp. Biol. Med* 2005;230:507–519.

Figure 1.

Right coronary blood flow is plotted for the normoxic baseline condition and for graded hypoxic conditions. Data were collected before and after adrenergic blockade. Values are mean $\pm$ SE. * $P < 0.05$ vs. baseline, same condition; § $P < 0.05$ vs. less severe hypoxia, same condition.

Figure 2.

Right coronary conductance is plotted for the normoxic baseline condition and for graded hypoxic conditions. Data were collected before and after adrenergic blockade. Values are mean $\pm$ SE. * $P < 0.05$ vs. baseline, same condition; § $P < 0.05$ vs. less severe hypoxia, same condition.

Figure 3.

Right coronary conductance is plotted as a function of right ventricular triple product for the untreated and adrenergic blockade conditions. Triple product increased during hypoxia for both conditions, but less so after adrenergic blockade. The slope of the relationship between conductance and triple product increased after adrenergic blockade. Values are mean $\pm$ SE. * $P < 0.05$ vs. normoxic baseline, same condition; § $P < 0.05$ vs. less severe hypoxia, same condition; # $P < 0.05$ vs. respective untreated condition.

Table 1

Blood gas variables at normoxia and during hypoxia

	Normoxia	Mild Hypoxia	Moderate Hypoxia	Severe Hypoxia	Probability Factor A Blockade	Probability Factor B Hypoxia	Interaction
Arterial PO₂ (mmHg)							
Untreated	87±3	71±2 [*]	46±1 ^{*§}	25±1 ^{*§}	0.9720	<0.0001	0.3420
Adrenergic Blockade	90±4	70±2 ^{*§}	45±1 ^{*§}	23±1 ^{*§}			
Arterial Hemoglobin (grams/100 ml blood)							
Untreated	12.7±0.5	12.4±0.5	12.4±0.6	13.2±0.6 ^{*§}	0.0015	0.0001	0.0680
Adrenergic Blockade	10.4±0.5 [#]	10.8±0.4 [#]	10.8±0.5 [#]	11.9±0.7 ^{*§#}			
Arterial Hematocrit (%)							
Untreated	40±2	40±2	39±2	41±2	0.0026	0.0014	0.0038
Adrenergic Blockade	33±2 [#]	34±1 [#]	35±2 [#]	39±2 ^{*§}			
Arterial O₂ Content (ml O₂/100 ml blood)							
Untreated	16.5±0.7	15.6±0.7 ^{*§}	12.6±0.7 ^{*§}	7.1±0.7 ^{*§}	<0.0001	<0.0001	0.0055
Adrenergic Blockade	13.7±0.6 [#]	13.4±0.6 [#]	10.8±0.8 ^{*§#}	5.9±0.7 ^{*§#}			
Right Coronary O₂ Delivery (μl O₂/min/g)							
Untreated	1039±73	1022±77	1223±92 ^{*§}	1302±135 [*]	0.0046	0.0007	0.8633
Adrenergic Blockade	771±70 [#]	808±71 [#]	930±92 [#]	1036±136 ^{*#}			
Arterial PCO₂ (mmHg)							
Untreated	31.6±1.2	32.5±2.1	30.9±1.8	26.8±3.0 ^{*§}	0.8248	0.0879	0.8558
Adrenergic Blockade	31.0±1.1	32.0±1.7	31.6±2.2	26.5±2.8 ^{*§}			
Arterial pH							
Untreated	7.45±0.01	7.45±0.02	7.46±0.03	7.51±0.04 ^{*§}	0.8965	0.0763	0.2955
Adrenergic Blockade	7.44±0.02	7.46±0.03	7.46±0.03	7.52±0.04 ^{*§}			
Arterial Glucose (mmol/l)							
Untreated	5.3±0.2	5.0±0.2	5.1±0.2	5.2±0.2	0.4712	0.3382	0.4228
Adrenergic Blockade	5.3±0.2	5.3±0.2	5.2±0.3	5.4±0.3			
Arterial Lactate (mmol/l)							
Untreated	1.1±0.2	0.9±0.1	1.0±0.2	1.5±0.2 ^{*§}	0.7590	0.0032	0.5440
Adrenergic Blockade	1.0±0.1	0.9±0.1	1.0±0.1	1.7±0.3 ^{*§}			

Values are mean ± SE for 7 dogs.

Factor A: Overall effect of Adrenergic Blockade (Phentolamine + Propranolol)

Factor B: Overall effect of Hypoxia

* $P < 0.05$ vs. baseline same group

§ $P < 0.05$ vs. less severe hypoxia same group

$P < 0.05$ vs. untreated group same condition.

Table 2

Hemodynamic data at normoxia and during hypoxia

	Normoxia (87/90) ^a	Mild Hypoxia (71/70) ^a	Moderate Hypoxia (46/45) ^a	Severe Hypoxia (25/23) ^a	Probability Factor A Blockade	Probability Factor B Hypoxia	Interaction
Mean Aortic Pressure (mmHg)							
Untreated	120±9	120±8	132±7*§	151±9*§	0.0093	<0.0001	0.3292
Adrenergic Blockade	108±5 [#]	108±5 [#]	112±6 [#]	138±8*§ [#]			
Heart Rate (bpm)							
Untreated	116±10	111±12	127±10 [§]	147±7*§	0.066	0.0058	0.5838
Adrenergic Blockade	101±6	104±6	110±6 [#]	132±10*§ [#]			
Right Systolic Ventricular Pressure (mmHg)							
Untreated	26±1	27±1	31±1	33±2	0.6536	0.0521	0.8757
Adrenergic Blockade	28±2	29±2	30±2	34±4			
Right Ventricular dP/dt_{max} (mmHg/s)							
Untreated	593±50	556±50	637±69	785±115*§	0.027	<0.0001	0.8014
Adrenergic Blockade	466±45	487±49	560±56	656±59*§ [#]			
Right Ventricular dP/dt_{min} (mmHg/s)							
Untreated	-703±144	-670±135	-748±158	-854±235	0.8230	0.6709	0.1505
Adrenergic Blockade	-702±143	-726±148	-752±141	-731±167			

Values are mean ± SE for 7 dogs, except only 6 dogs provided data for variables involving RV pressure.

Factor A: Overall effect of Adrenergic Blockade (Phentolamine + Propranolol)

Factor B: Overall effect of Hypoxia

^aMean respective arterial PO₂ for Normoxic and Adrenergic Blockade conditions (see Table 1);

* $P < 0.05$ vs. baseline same group

§ $P < 0.05$ vs. less severe hypoxia same group

[#] $P < 0.05$ vs. untreated group same condition