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ORIGINAL CONTRIBUTION

Oxygen-sensing pathways below autoregulatory threshold act to sustain myocardial oxygen delivery during reductions in perfusion pressure

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Abstract

The coronary circulation has an innate ability to maintain constant blood flow over a wide range of perfusion pressures. However, the mechanisms responsible for coronary autoregulation remain a fundamental and highly contested question. This study interrogated the local metabolic hypothesis of autoregulation by testing the hypothesis that hypoxemia-induced exaggeration of the metabolic error signal improves the autoregulatory response. Experiments were performed on open-chest anesthetized swine during stepwise changes in coronary perfusion pressure (CPP) from 140 to 40 mmHg under normoxic (n = 15) and hypoxemic (n = 8) conditions, in the absence and presence of dobutamine-induced increases in myocardial oxygen consumption (MVO_2) (n = 5–7). Hypoxemia ($PaO_2 < 40$ mmHg) decreased coronary venous PO_2 ($CvPO_2$) ~ 30% ($P < 0.001$) and increased coronary blood flow ~ 100% ($P < 0.001$), sufficient to maintain myocardial oxygen delivery ($P = 0.14$) over a wide range of CPPs. Autoregulatory responsiveness during hypoxemia-induced reductions in $CvPO_2$ were associated with increases of autoregulatory gain (Gc; $P = 0.033$) but not slope ($P = 0.585$) over a CPP range of 120 to 60 mmHg. Preservation of autoregulatory Gc ($P = 0.069$) and slope ($P = 0.264$) was observed during dobutamine administration ± hypoxemia. Reductions in coronary resistance in response to decreases in CPP predominantly occurred below $CvPO_2$ values of ~ 25 mmHg, irrespective of underlying vasomotor reserve. These findings support the presence of an autoregulatory threshold under which oxygen-sensing pathway(s) act to preserve sufficient myocardial oxygen delivery as CPP is reduced during increases in MVO_2 and/or reductions in arterial oxygen content.

Keywords Hypoxia · Feedback · Oxygen consumption · Homeostasis · Coronary circulation

Introduction

The coronary circulation is regulated by numerous mechanisms that act to ensure myocardial oxygen delivery matches the level of myocardial oxygen consumption (MVO_2) [27, 45, 53]. This balance between coronary blood flow and myocardial metabolism is preserved over a variety of pathophysiologic perturbations, including reductions in perfusion pressure which occur distal to sites of atherosclerotic lesions. The ability of the coronary circulation to maintain constant blood flow as perfusion pressure is decreased, i.e., coronary pressure-flow autoregulation [1, 26, 31, 45], is an essential phenomenon that serves to mitigate hypoperfusion, cardiac dysfunction, and overt ischemic injury [12, 26, 33, 34, 37]. Despite the crucial nature of this intrinsic response, understanding of the mechanisms responsible for autoregulation

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remains one of the most fundamental questions in the field of coronary physiology to this day.

Primary theories to explain coronary autoregulatory behavior largely focus on local metabolic vs. myogenic mechanisms [38]. The local metabolic hypothesis proposes that vasoactive end products serve as a link between coronary blood flow and MVO_2 as myocardial oxygen tension decreases with reductions in perfusion pressure [2, 7, 14, 30, 55]. Alternatively, decreases in intraluminal pressure elicit an intrinsic myogenic response that produces vasorelaxation and reductions in microvascular resistance [4, 10, 37, 40, 42]. Importantly, these mechanisms share common end-effector pathways, thus, demonstration that inhibition of $Ca_V1.2$ channels abolishes coronary autoregulation [7] can be interpreted to support the contribution of either the metabolic and/or myogenic hypotheses. Accordingly, the competing nature of these influences continues to fuel debate around the relative contribution of these pathways to this phenomenon.

To address the confounding nature of the proposed mechanisms of the autoregulatory response, our group recently challenged the local metabolic hypothesis by utilizing hemodilution (anemia) ± dobutamine to separate changes in the proposed local metabolic error signal (i.e., myocardial tissue PO_2) [27] from alterations in underlying MVO_2 and coronary vasomotor tone. Based on the assumption that coronary venous PO_2 ($CvPO_2$) provides an accurate estimate of myocardial oxygenation [15, 27], Kiel et al. determined that autoregulation was essentially absent during hemodilution (~ 50% reduction in hematocrit) and dobutamine-induced increases in MVO_2, despite relatively unchanged (normal) values of $CvPO_2$ [38]. Alternatively, coronary vasomotor tone, assessed by coronary zero-flow pressure (Pzf) [17, 18, 20, 49, 56], was positively correlated with changes in coronary flow and overall autoregulatory capacity. As such, changes in coronary blood flow were the greatest, and autoregulatory capability the lowest, when values of Pzf fell below a threshold value of ~ 20 mmHg. While these findings are consistent with a myogenic-dependent mechanism of coronary pressure-flow autoregulation, a role for local metabolic pathways was not ruled out [38].

The present investigation was designed to further interrogate the local metabolic hypothesis of autoregulation by examining coronary pressure-flow responses before and during hypoxemia-induced exaggeration of the proposed metabolic error signal [21, 52]. Our rationale was based on prior demonstration that reductions in PaO_2 (< 40 mmHg) reliably increase coronary blood flow and reduce $CvPO_2$ across species [51, 52]. We hypothesized that if myocardial tissue PO_2 (reflected in $CvPO_2$) influences the degree of autoregulation, then hypoxemia should improve autoregulatory responsiveness, despite underlying reductions in coronary microvascular resistance. In contrast, if autoregulatory behavior is primarily modulated by pressure-dependent (i.e., myogenic) alterations in vasomotor tone, then reductions coronary resistance produced by dobutamine and/or hypoxemia will be associated with reductions in the coronary autoregulatory response, irrespective of changes in $CvPO_2$. Data from these experiments offer novel insight into the complex mechanisms that contribute to coronary pressure-flow autoregulation.

Methods

This investigation was approved by the University of North Texas Health Science Center Institutional Animal Care and Use Committee and performed in accordance with the Guide for the Care and Use of Laboratory Animals (NIH Publication No. 85–23, Revised 2011). Domestic (Yorkshire) swine (~ 50 kg; n = 15) were sedated with Telazol, xylazine, and ketamine (5.0, 2.5, and 2.5 mg/kg, im) prior to anesthesia with buprenorphine (0.03 mg/kg, im) and α-chloralose (60 mg/kg, iv). Additional α-chloralose (20 mg/kg, iv) was given hourly to maintain anesthesia.

Experimental preparation

Anesthetized swine were intubated and ventilated with O_2-supplemented room air to achieve > 95% oxyhemoglobin saturation and an end tidal CO_2 of ~ 40 mmHg; measured by aural pulse oximetry and inline capnography. Bilateral femoral cut downs were performed, and catheters placed in both femoral arteries and one femoral vein. One femoral artery catheter provided continuous measurement of systemic blood pressure and heart rate, while the venous catheter allowed for administration of drugs (supplemental α-chloralose, heparin, and dobutamine). The other femoral artery catheter supplied blood to an extracorporeal servo-controlled pump used to perfuse the left anterior descending (LAD) coronary artery at designated perfusion pressures, as previously described by our laboratory [7].

Succinylcholine (0.5 mg/kg, iv) was administered, followed by a left lateral thoracotomy in the fifth intercostal space and the pericardium incised to expose the heart. Following isolation of the LAD and the administration of heparin (500 units/kg, iv), the LAD was cannulated with a steel tip cannula fed by the extracorporeal perfusion circuit. Coronary perfusion pressure (CPP) was regulated by a servo-controlled roller pump and coronary blood flow was continuously measured by an in-line flow transducer (Transonic Systems, Ithaca, NY, USA). The anterior interventricular vein was catheterized to sample coronary venous blood from the LAD perfusion territory.

Experimental protocol

Pigs were randomly assigned to one of the following experimental groups: (1) normoxia followed by hypoxemia (n = 8; n = 6 female); or (2) normoxia followed by intravenous dobutamine (10 µg/kg/min, n = 7) ± hypoxemia (n = 5; n = 4 female); with n = 2 pigs not completing the dobutamine + hypoxemia protocol. Hypoxemia was induced by titrating nitrogen gas into the ventilation line to reduce the partial pressure of oxygen and achieve a stable level of hypoxemia (PaO_2 of < 40 mmHg).

Following a ~ 15 min stabilization period, normoxic pressure-flow autoregulation was assessed by reducing CPP in increments of 20 mmHg from 140 to 40 mmHg. Arterial and coronary venous blood samples were collected simultaneously once hemodynamic parameters stabilized at that CPP. Coronary Pzf was assessed by clamping the perfusion circuit and allowing coronary blood flow to cease for ~ 4 s as previously described by our lab [38]. Upon reaching a CPP of 40 mmHg under normoxic conditions, CPP was returned to 140 mmHg and the protocol repeated in the presence of (1) hypoxemia alone (n = 8) or (2) dobutamine alone (n = 7) followed by dobutamine and hypoxemia (n = 5). Ample stabilization periods (~ 15 min) were provided between each experimental condition to allow sufficient time for blood within the extracorporeal perfusion circuit (deadspace ~ 13 mL) to equilibrate with that of the systemic circulation. Following completion of experiments, animals were euthanized by electrical fibrillation followed by excision of the heart.

As previously reported by our laboratory and others [1, 2, 11], closed-loop autoregulatory gain (Gc) was calculated from the following formula:

$$Gc = 1 - ((\Delta F/F)/(\Delta CPP/CPP))$$

where $\Delta F/F = ((F_{120} - F_{60})/F_{120})$ and $\Delta CPP/CPP = ((CPP_{120} - CPP_{60})/CPP_{120})$ represent the changes from a given flow (F) and perfusion pressure (CPP) over a CPP range of 120 mmHg to 60 mmHg [38]. A Gc value of 1 reflects perfect autoregulation, and values < 0 indicate no autoregulation. Autoregulatory slope was assessed by dividing the change in coronary flow by the change in $CPP = (F_{120} - F_{60})/(CPP_{120} - CPP_{60})$. Coronary vascular resistance was calculated by dividing CPP by coronary blood flow.

Blood gas analyses

Arterial and coronary venous blood samples were collected, immediately sealed, and placed on ice. The samples were analyzed for pH, PCO_2, PO_2, hemoglobin saturation, lactate, and oxygen content with an automatic blood gas analyzer and CO-oximeter system (Instrumentation Laboratories, Bedford, MA, USA). LAD perfusion territory was estimated to be 30% of total heart weight, as previously described [28]. Myocardial oxygen extraction was determined by the difference between arterial and coronary venous oxygen content divided by arterial oxygen content, multiplied by 100. MVO_2 was calculated by multiplying coronary blood flow by the coronary arterial-coronary venous difference in oxygen content.

Statistical analysis

Data are presented as mean ± SEM. Statistical comparisons for data presented in Tables 1 and 2 were made by a two-way analysis of variance (ANOVA; Factor A: CPP; Factor B: Condition). Differences were considered statistically significant when ($P < 0.05$). If statistical significance was detected with ANOVA, a Holm-Šídák post hoc analysis was performed. A Paired t-test was utilized to compare autoregulatory gain and slope in control (normoxic) vs. hypoxemic conditions and one-way analysis of variance comparing normoxia to dobutamine with and without hypoxemia. Pearson correlation analysis was utilized to assess the relationship between Gc and slope values relative to their respective baseline $CvPO_2$ at CPP = 100 mmHg. Lines of best fit are shown for significant associations with correlation coefficients (r) > 0.40. Statistical analyses were performed with Prism 9.4.1 software (GraphPad Software).

Results

Effects of hypoxemia on coronary pressure-flow autoregulation

Hemodynamic and blood gas responses to changes in CPP in swine before and during hypoxemia (n = 8) are provided in Table 1. Reducing PaO_2 to 34 ± 1 mmHg ($P < 0.001$) reduced blood pressure ~ 25% ($P < 0.001$) and increased heart rate ~ 30% ($P = 0.003$), presumably via a chemoreflex-mediated autonomic response. Reductions in arterial pH ($P = 0.027$) under hypoxemic conditions were associated with an approximate doubling of arterial lactate concentration ($P < 0.001$), albeit with no change in $PaCO_2$ ($P = 0.529$) or myocardial lactate uptake ($P = 0.215$).

Coronary blood flow responses to reductions in CPP before and during hypoxemic conditions are shown in Fig. 1a. Hypoxemia significantly increased coronary blood flow ~ 100% across CPPs ranging from 140 to 40 mmHg ($P < 0.001$). The approximate 20% increase in MVO_2 associated with hypoxemia ($P = 0.030$; Fig. 1c) was accompanied by marked reductions in $CvPO_2$ ($P < 0.001$; Fig. 1d) and coronary venous oxygen saturation ($P < 0.001$; Table 1) across the entire range of CPP. The marked vasodilation

Table 1 Hemodynamic and blood gas parameters during normoxia and hypoxemia

Coronary perfusion pressure (mmHg)	140	120	100	80	60	40	Condition
Mean arterial pressure (mmHg)							
Normoxia	99 ± 6	99 ± 5	97 ± 5	96 ± 5	95 ± 5	94 ± 5	P < 0.001
Hypoxemia	77 ± 6*	73 ± 6*	72 ± 6*	72 ± 5*	72 ± 5*	70 ± 4*	
Heart rate (beats/min)							
Normoxia	86 ± 7	86 ± 7	89 ± 7	89 ± 7	91 ± 9	91 ± 8	P = 0.003
Hypoxemia	111 ± 7*	112 ± 7*	114 ± 8*	115 ± 9*	121 ± 10*	125 ± 11*	
Hematocrit (%)							
Normoxia	30 ± 1	29 ± 1	29 ± 1	29 ± 1	29 ± 1	29 ± 1	P = 0.006
Hypoxemia	31 ± 1	31 ± 1*	32 ± 1*	32 ± 1*	33 ± 1*	33 ± 1*	
Arterial pH							
Normoxia	7.48 ± 0.01	7.47 ± 0.01	7.47 ± 0.01	7.47 ± 0.01	7.47 ± 0.01	7.48 ± 0.01	P = 0.027
Hypoxemia	7.46 ± 0.01*	7.46 ± 0.01*	7.45 ± 0.01*	7.44 ± 0.02*	7.44 ± 0.02*	7.42 ± 0.03*	
PaO_2 (mmHg)							
Normoxia	130 ± 6	135 ± 5	138 ± 7	136 ± 6	138 ± 7	135 ± 7	P < 0.001
Hypoxemia	34 ± 1*	34 ± 1*	34 ± 1*	34 ± 1*	33 ± 1*	33 ± 2*	
$PaCO_2$ (mmHg)							
Normoxia	39 ± 1	40 ± 1	40 ± 1	40 ± 1	40 ± 1	39 ± 1	P = 0.529
Hypoxemia	39 ± 1	39 ± 1	39 ± 1	39 ± 1	39 ± 1	40 ± 1	
Lactate (mM)							
Normoxia	1.6 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	P < 0.001
Hypoxemia	2.8 ± 0.2*	3.1 ± 0.2*	3.4 ± 0.3*	3.7 ± 0.3*	3.8 ± 0.3*	4.0 ± 0.4*	
Lactate uptake (µmol/min/g)							
Normoxia	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.2 ± 0.1	P = 0.215
Hypoxemia	0.7 ± 0.2	0.4 ± 0.2	0.5 ± 0.2	0.6 ± 0.1	0.4 ± 0.2	-0.2 ± 0.2	
Pzf (mmHg)							
Normoxia	28 ± 3	23 ± 3	23 ± 3	19 ± 2	16 ± 2	10 ± 1	P = 0.003
Hypoxemia	18 ± 1*	17 ± 2	15 ± 2*	12 ± 1*	10 ± 2*	8 ± 1*	
CvO_2 Hbg saturation (%)							
Normoxia	53 ± 3	47 ± 4	36 ± 4	27 ± 3	22 ± 2	18 ± 1	P < 0.001
Hypoxemia	25 ± 3*	23 ± 3*	19 ± 3*	15 ± 2*	11 ± 2*	9 ± 1*	
Oxygen extraction (%)							
Normoxia	48 ± 3	54 ± 4	65 ± 4	73 ± 3	78 ± 2	82 ± 1	P < 0.001
Hypoxemia	57 ± 3*	60 ± 4*	67 ± 3	72 ± 2	79 ± 2	83 ± 1	

*$P < 0.05$ vs Normoxia at the same CPP; Normoxia (n = 8); Hypoxemia (n = 8)

corresponded with significant reductions in coronary Pzf ($P = 0.003$; Table 1) and was sufficient to maintain myocardial oxygen delivery across the entire range of CPPs ($P = 0.140$; Fig. 1b).The slope of the relationship between coronary blood flow and MVO_2 was similar between normoxic and hypoxemic conditions ($P = 0.842$, r = 0.972; Fig. 2a), while hypoxemia significantly diminished $CvPO_2$ relative to modest differences in MVO_2 ($P < 0.001$; Fig. 2b).

Paired comparisons of autoregulatory responsiveness before and during hypoxemia revealed a significant increase in autoregulatory Gc ($P = 0.033$; Fig. 3a) but not slope ($P = 0.585$; Fig. 3c) over a CPP range of 120 to 60 mmHg. Further examination of the autoregulatory responsiveness revealed a significant inverse association between Gc (CPP range from 120 to 60 mmHg) and $CvPO_2$ (measured at CPP of 100 mmHg) under normoxic and hypoxemic conditions ($P = 0.001$, r = – 0.737; Fig. 3b). A minor positive correlation between autoregulatory slope and $CvPO_2$ (measured at CPP of 100 mmHg) was also detected during normoxia and hypoxemia ($P = 0.004$, r = 0.367; Fig. 3d). Alterations in the autoregulatory response produced by hypoxemia are unlikely to be related to repeated exposure to reductions in CPP as additional time control experiments (n = 3) revealed no differences in coronary blood flow ($P = 0.24$) in swine subjected to consecutive reductions in CPP from 140 to 40 mmHg (data not shown).

Table 2 Hemodynamic and blood gas parameters during normoxia, dobutamine, and hypoxemia plus dobutamine

Coronary perfusion pressure (mmHg)	140	120	100	80	60	40	Condition
Mean arterial pressure (mmHg)							
Normoxia	96 ± 3	92 ± 2	90 ± 2	88 ± 3	85 ± 3	84 ± 3	P = 0.003
Normoxia + Dobutamine	90 ± 6	84 ± 4	83 ± 4	82 ± 5	81 ± 5	83 ± 3	
Hypoxemia + Dobutamine	77 ± 9*	72 ± 8*	69 ± 7*	67 ± 7*	64 ± 7*	62 ± 7*	
Heart rate (beats/min)							
Normoxia	96 ± 8	102 ± 11	103 ± 10	104 ± 10	104 ± 10	104 ± 10	P < 0.001
Normoxia + Dobutamine	158 ± 13*	166 ± 12*	167 ± 12*	167 ± 11*	165 ± 10*	157 ± 14*	
Hypoxemia + Dobutamine	159 ± 7*	161 ± 5*	160 ± 5*	161 ± 5*	156 ± 3*	159 ± 4*	
Hematocrit (%)							
Normoxia	28 ± 2	27 ± 1	28 ± 1	28 ± 2	28 ± 1	28 ± 2	P < 0.001
Normoxia + Dobutamine	37 ± 1*	37 ± 1*	37 ± 1*	38 ± 1*	38 ± 1*	38 ± 1*	
Hypoxemia + Dobutamine	38 ± 2*	39 ± 2*	38 ± 2*	38 ± 2*	37 ± 2*	38 ± 2*	
Arterial pH							
Normoxia	7.45 ± 0.02	7.44 ± 0.02	7.45 ± 0.02	7.45 ± 0.03	7.45 ± 0.03	7.45 ± 0.02	P = 0.048
Normoxia + Dobutamine	7.41 ± 0.02	7.41 ± 0.02	7.40 ± 0.02	7.40 ± 0.02	7.40 ± 0.02	7.40 ± 0.02	
Hypoxemia + Dobutamine	7.41 ± 0.02	7.41 ± 0.02	7.41 ± 0.01	7.40 ± 0.01	7.40 ± 0.02	7.40 ± 0.01	
PaO_2 (mmHg)							
Normoxia	136 ± 12	137 ± 11	137 ± 12	138 ± 11	137 ± 11	137 ± 11	P < 0.001
Normoxia + Dobutamine	121 ± 11	120 ± 9	117 ± 10	117 ± 10	121 ± 8	120 ± 8	
Hypoxemia + Dobutamine	38 ± 2*†	37 ± 2*†	36 ± 1*†	36 ± 1*†	36 ± 2*†	36 ± 2*†	
$PaCO_2$ (mmHg)							
Normoxia	42 ± 1	42 ± 1	42 ± 2	42 ± 2	42 ± 2	42 ± 2	P = 0.116
Normoxia + Dobutamine	44 ± 2	44 ± 2	45 ± 2	44 ± 2	45 ± 2	44 ± 2	
Hypoxemia + Dobutamine	42 ± 1	43 ± 2	44 ± 1	43 ± 1	43 ± 2	43 ± 1	
Lactate (mM)							
Normoxia	1.9 ± 0.4	1.9 ± 0.4	1.8 ± 0.4	1.8 ± 0.4	1.8 ± 0.3	1.8 ± 0.3	P = 0.034
Normoxia + Dobutamine	1.5 ± 0.2	1.5 ± 0.2	1.6 ± 0.3	1.6 ± 0.3	1.7 ± 0.3	1.7 ± 0.3	
Hypoxemia + Dobutamine	2.4 ± 0.4	2.7 ± 0.5	2.8 ± 0.5	3.1 ± 0.7	3.4 ± 0.8	3.6 ± 0.9	
Lactate uptake (μmol/min/g)							
Normoxia	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.1 ± 0.1	P = 0.107
Normoxia + Dobutamine	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.3 ± 0.1	0.0 ± 0.05	− 0.6 ± 0.2	
Hypoxemia + Dobutamine	0.1 ± 0.3	0.2 ± 0.3	0.1 ± 0.1	− 0.1 ± 0.3	− 0.6 ± 0.5	− 1.2 ± 0.7	
Pzf (mmHg)							
Normoxia	17 ± 2	16 ± 2	14 ± 2	12 ± 1	9 ± 1	7 ± 1	
Normoxia + Dobutamine	12 ± 1	11 ± 1	11 ± 1	10 ± 1	8 ± 1	6 ± 1	P = 0.004
Hypoxemia + Dobutamine	9 ± 2*	8 ± 2*	6 ± 1*	5 ± 1*	4 ± 2*	3 ± 2*	
CvO_2 Hbg saturation (%)							
Normoxia	61 ± 4	54 ± 3	46 ± 3	40 ± 4	35 ± 3	25 ± 2	
Normoxia + Dobutamine	52 ± 2	44 ± 3	38 ± 3	30 ± 3	25 ± 2	18 ± 1	P < 0.001
Hypoxemia + Dobutamine	24 ± 2*	18 ± 2*	16 ± 2*	12 ± 2*	10 ± 1*	8 ± 1*	
Oxygen extraction (%)							
Normoxia	40 ± 4	46 ± 3	53 ± 3	60 ± 4	65 ± 3	75 ± 2	
Normoxia + Dobutamine	48 ± 2	56 ± 3*	61 ± 3	69 ± 3*	75 ± 2*	81 ± 1	P < 0.001
Hypoxemia + Dobutamine	61 ± 1	69 ± 4*†	71 ± 3	78 ± 3*†	82 ± 2*†	86 ± 1	

*$P < 0.05$ vs Normoxia at the same CPP; †$P < 0.05$ vs Normoxia + Dobutamine at the same CPP; Normoxia (n = 7); Dobutamine (n = 7), and Hypoxemia + Dobutamine (n = 5)

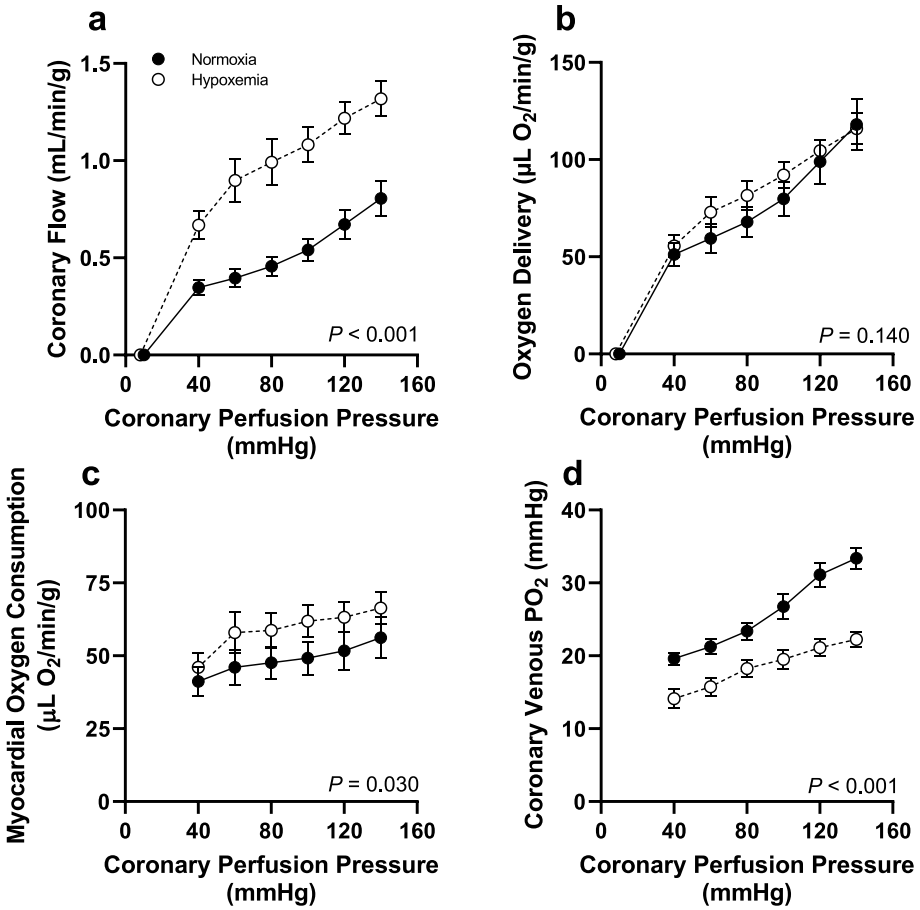

Fig. 1 Effects of hypoxemia on myocardial oxygen delivery and metabolism. Average responses from paired studies in the absence and presence of hypoxemia (n = 8) as CPP was reduced from 140 to 40 mmHg. **a** Hypoxemia increased coronary blood flow at any given level of CPP. **b** Oxygen delivery was similar between normoxic and hypoxemic conditions as CPP was reduced. **c** Hypoxemia was accompanied by a modest increase in MVO_2. **d** $CvPO_2$, an index of myocardial oxygenation, was decreased by hypoxemia across all CPPs

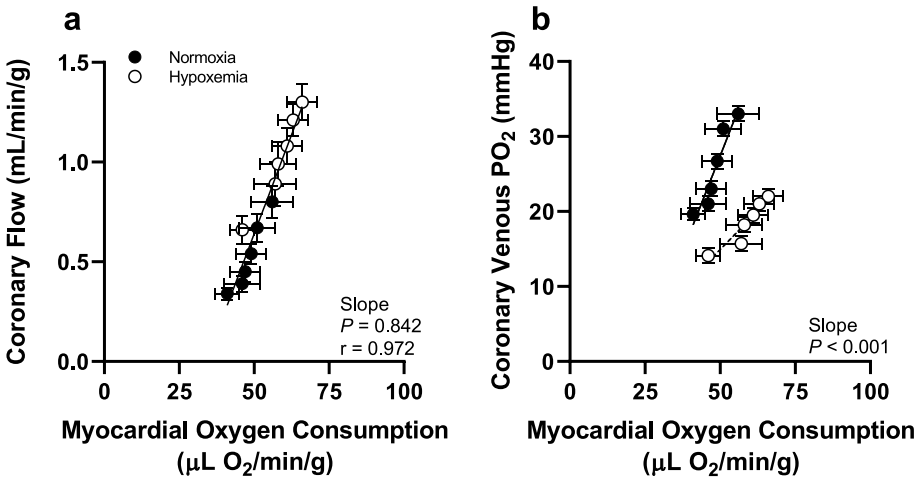

Fig. 2 Effects of hypoxemia on the balance between coronary flow and myocardial metabolism. Average responses from paired studies in the absence and presence of hypoxemia (n = 8) as CPP was reduced from 140 to 40 mmHg. **a** Hypoxemia increased coronary blood flow and MVO_2, but did not affect the slope of the relationship between coronary blood flow and MVO_2. **b** Hypoxemia decreased the slope of the relationship between $CvPO_2$ and MVO_2

Dobutamine, hypoxemia and degree of coronary autoregulation

To further interrogate underlying mechanisms of coronary pressure-flow autoregulation, additional experiments were performed during dobutamine-mediated increases in MVO_2, under both normoxic and hypoxemic conditions. Although these experiments were performed in same animals, the number of pigs in the treatment groups differ because 2 of the 7 pigs that underwent the protocol did not survive the dobutamine + hypoxemia condition. We found that dobutamine significantly increased heart rate (~ 60%) ($P < 0.001$), but mean arterial pressure was unchanged (Table 2). The combination of hypoxemia (PaO_2 to 36–38 mmHg) plus dobutamine did not further influence heart rate, but mean arterial pressure was decreased by ~ 20% ($P = 0.003$) and

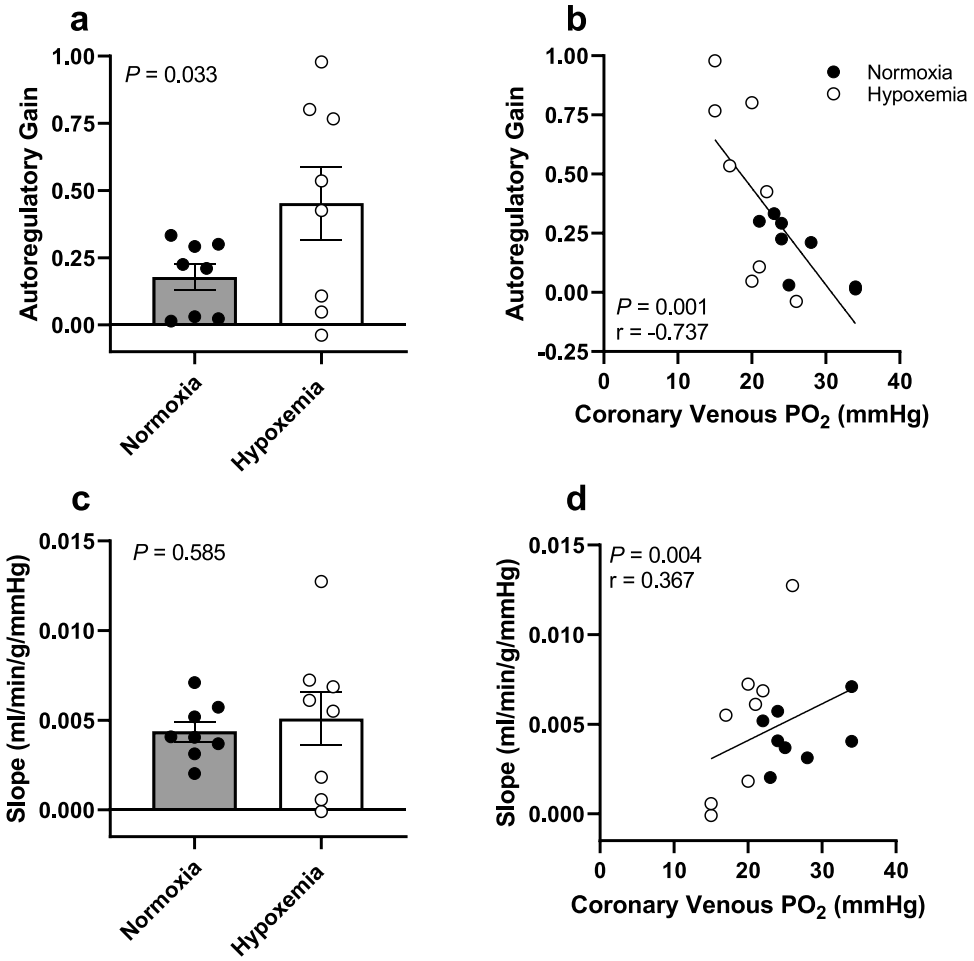

Fig. 3 Effect of Hypoxemia and $CvPO_2$ on coronary autoregulatory capacity. Individual data from paired studies in the absence and presence of hypoxemia (n = 8) over CPP range of 120 to 60 mmHg. **a** Hypoxemia significantly increased Gc. **b** Coronary Gc (CPP 120 to 60 mmHg) was inversely related to $CvPO_2$ (taken at CPP = 100 mmHg). **c** Slope of relationship between coronary blood flow and CPP (range 120 – 60 mmHg) was unaffected by hypoxemia. **d** There was a minor association between the slope relationship of coronary blood flow versus CPP (range 120– 60 mmHg) and $CvPO_2$ (taken at CPP = 100 mmHg)

circulating arterial lactate concentration increased, especially at CPPs ≤ 80 mmHg ($P = 0.034$; Table 2). Dobutamine administration was also associated with an ~ 160% increase in MVO_2 ($P < 0.001$) and an ~ 35% increase in hematocrit ($P < 0.001$).

Coronary blood flow responses to reductions in CPP before and during dobutamine with and without inducing hypoxemia are shown in Fig. 4a. Administration of dobutamine in the absence and presence of hypoxemia significantly increased coronary blood flow as CPP was reduced from 140 to 40 mmHg ($P = 0.001$). The marked vasodilation under both conditions corresponded with significant reductions in coronary Pzf ($P = 0.004$; Table 2) and significant increases in myocardial oxygen delivery across the entire range of CPPs ($P = 0.002$; Fig. 4b). Administration of dobutamine with and without hypoxemia significantly increased MVO_2 ($P < 0.001$; Fig. 4c), however, $CvPO_2$ was reduced ($P < 0.001$) relative to normoxic control swine, only in the presence of hypoxemia (Fig. 4d). Dobutamine with and without hypoxemia reduced the slope of the relationship between coronary blood flow ($P = 0.031$; Fig. 5a) and $CvPO_2$ ($P < 0.001$; Fig. 5b) relative to MVO_2 across the entire range of CPPs studied. Autoregulatory Gc ($P = 0.069$; Fig. 6a) and slope ($P = 0.264$; Fig. 6c) over a CPP range of 120 to 60 mmHg were unaffected by dobutamine in the absence or presence of hypoxemia ($PaO_2 \leq 40$ mmHg). While a significant inverse association between autoregulatory capability (Gc) and $CvPO_2$ (measured at CPP of 100 mmHg) was detected under dobutamine-induced increases in $MVO_2 \pm$ hypoxemic conditions ($P < 0.001$, r = – 0.722; Fig. 6b), no such correlation was observed between autoregulatory slope and $CvPO_2$ (measured at CPP of 100 mmHg) ($P = 0.252$, r = 0.285; Fig. 6d).

Coronary autoregulation and $CvPO_2$

To further examine the metabolic hypothesis of coronary pressure-flow autoregulation, average values of coronary resistance (CPP range of 120 to 60 mmHg) were plotted relative to their respective average $CvPO_2$ for each of the experimental conditions in this study (Fig. 7a). This relationship revealed that decreases in $CvPO_2$, that accompanied reductions in CPP in each of the groups (Fig. 1d and Fig. 4d), were not associated with changes

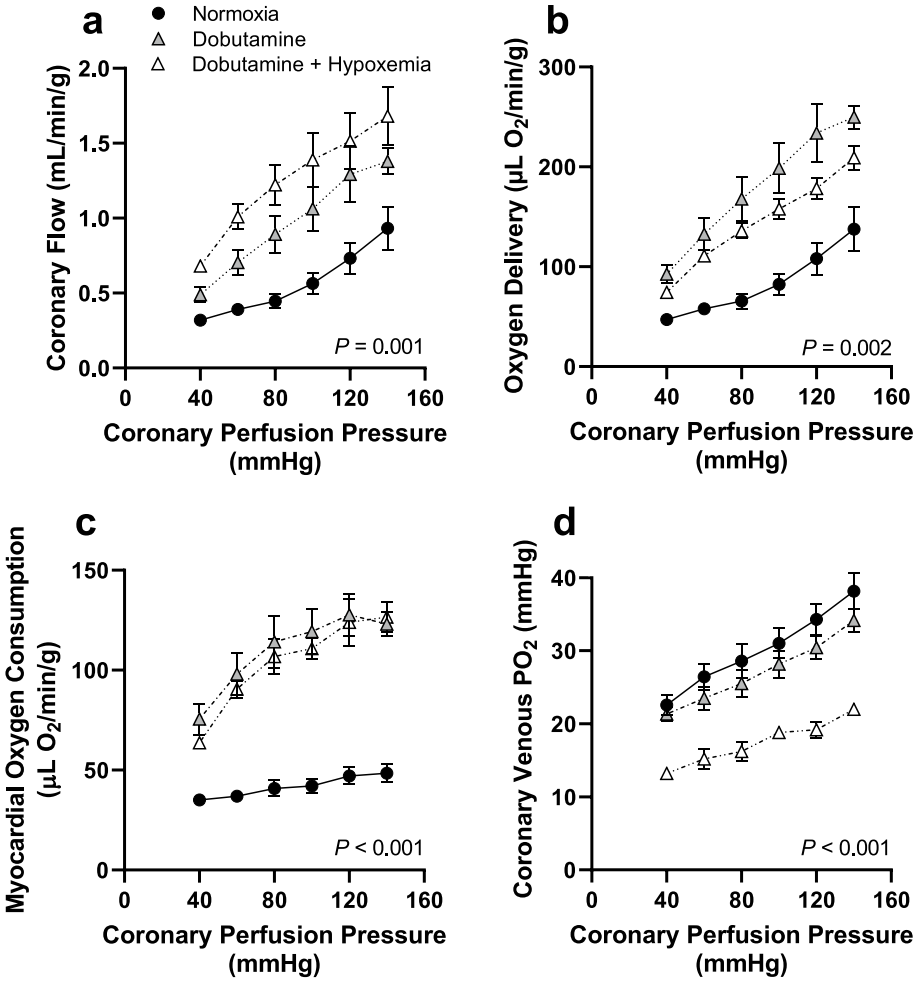

Fig. 4 Effects of Dobutamine ± Hypoxemia on myocardial oxygen delivery and metabolism. Average responses from studies during Normoxia (n = 7), Dobutamine (n = 7), and Dobutamine + Hypoxemia (n = 5) as CPP is reduced from 140 to 40 mmHg. **a** Dobutamine and Dobutamine + Hypoxemia significantly increased coronary blood flow at any given level of CPP. **b** Oxygen delivery was increased by Dobutamine and Dobutamine + Hypoxemia. **c** MVO_2 was increased to a similar extent by Dobutamine and Dobutamine + Hypoxemia. **d** Dobutamine did not significantly affect $CvPO_2$, however the addition of Hypoxemia to Dobutamine markedly lowered $CvPO_2$ at any given level of CPP

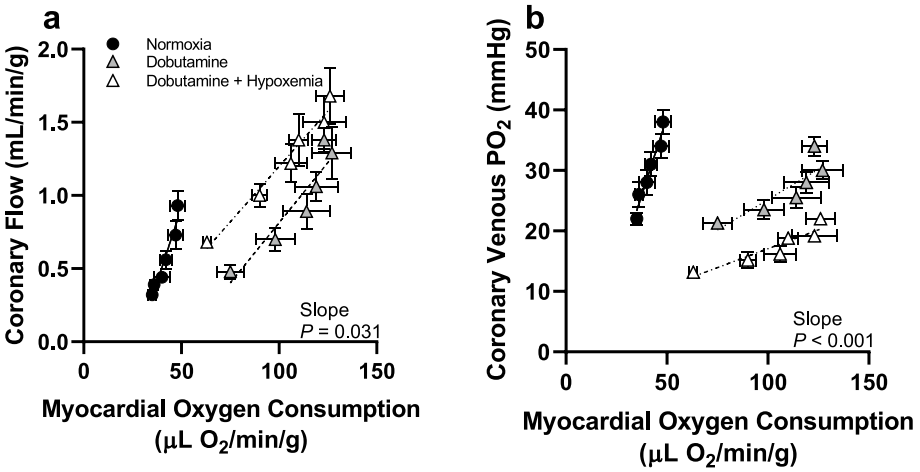

Fig. 5 Effects of Dobutamine ± Hypoxemia on the balance between coronary flow and myocardial metabolism. Average responses from studies during Normoxia (n = 7), Dobutamine (n = 7), and Dobutamine + Hypoxemia (n = 5) as CPP is reduced from 140 to 40 mmHg. **a** Slope of the relationship between coronary blood flow was significantly reduced by Dobutamine and Dobutamine + Hypoxemia. **b** Slope of the relationship between $CvPO_2$ and MVO_2 was diminished by Dobutamine and Dobutamine + Hypoxemia

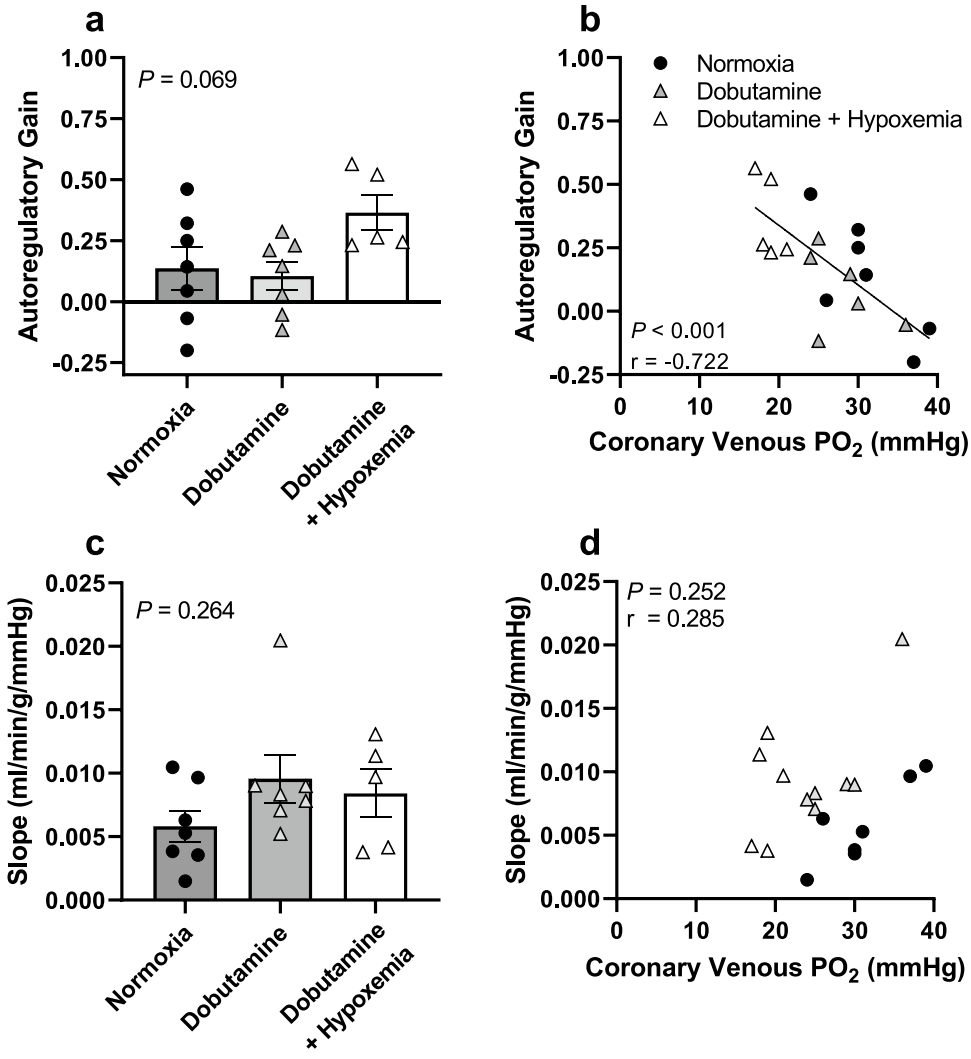

Fig. 6 Effects of Dobutamine ± Hypoxemia and $CvPO_2$ on coronary autoregulatory capacity. Individual data from paired studies during Normoxia (n = 7), Dobutamine (n = 7), and Dobutamine + Hypoxemia (n = 5) over CPP range of 120 to 60 mmHg. **a** Coronary Gc (CPP 120 – 60 mmHg) was unaffected by dobutamine ± hypoxemia. **b** Coronary Gc (CPP 120 – 60 mmHg) was strongly inversely related to $CvPO_2$ (taken at CPP = 100 mmHg). **c** Slope of relationship between coronary blood flow and CPP (range 120 – 60 mmHg) was unaffected by dobutamine ± hypoxemia. **d** Slope of the relationship between coronary blood flow and CPP (range 120 – 60 mmHg) was not associated with $CvPO_2$ (taken at CPP = 100 mmHg)

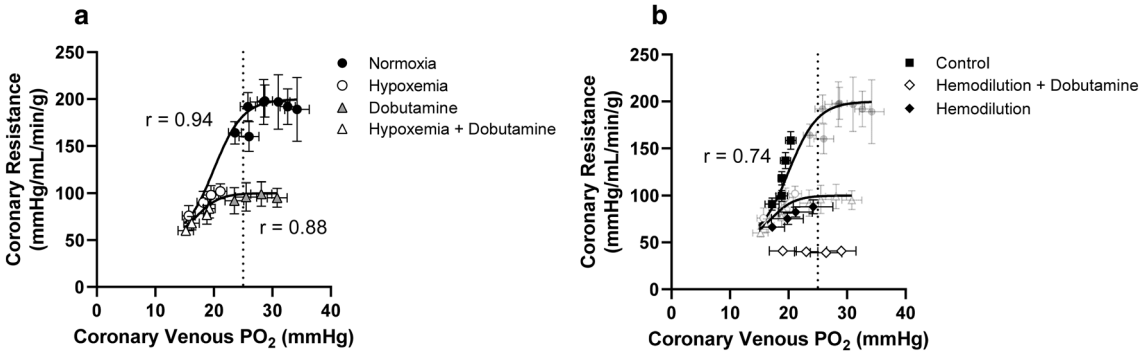

Fig. 7 Relationship between coronary vascular resistance and $CvPO_2$. **a** Average data from each experimental group (Normoxia (n = 8); Hypoxemia (n = 8); Normoxia (n = 7); Dobutamine (n = 7); Dobutamine + Hypoxemia (n = 5)) as CPP was reduced from 120 to 60 mmHg. Coronary resistance remained unchanged, irrespective of underlying condition, until $CvPO_2$ fell below ~ 25 mmHg. Below this apparent threshold, the slope of the relationship between coronary vascular resistance and $CvPO_2$ was steepened. **b** Shadow data from average group responses in Panel a; Control data with strong autoregulatory Gc from Stepp et al. [50]; Hemodilution and Hemodilution + Dobutamine data with poor Gc from Kiel et al. [38]. Average data from the strong autoregulatory group are consistent with the predicted relationship between coronary resistance and $CvPO_2$. A similar relationship between coronary resistance and $CvPO_2$ is observed during hemodilution (~ 50% reduction in hematocrit) and hypoxemia. Alternatively, no change in coronary resistance is observed in the poor autoregulatory group (Hemodilution + Dobutamine), with low coronary resistance, regardless of change in $CvPO_2$

in coronary resistance until $CvPO_2$ fell below a relative threshold of ~ 25 mmHg. For the normoxia hypoxemia ± dobutamine curve, r = 0.94, while r = 0.88 for the dobutamine and hypoxemia + dobutamine curve. Thus, reductions in CPP were accompanied by little change in coronary resistance during normoxia and dobutamine infusion, where values of $CvPO_2$ remained largely ≥ 25 mmHg (Fig. 7a), regardless of underlying experimental condition. Further analysis of this relationship was also performed by the addition of data from prior studies that demonstrated strong (Gc = 0.99; [50]) vs. poor (Gc = −0.02; [38]) autoregulatory gain (Fig. 7b). Average data from the strong autoregulatory group are consistent with the predicted relationship between coronary resistance and $CvPO_2$, with curve fit of r = 0.74. Data from our prior study by Kiel et al. [38] reveal a similar relationship between coronary resistance and $CvPO_2$ during hemodilution (~ 50% reduction in hematocrit) and hypoxemia (Fig. 7b). Alternatively, no change in coronary resistance is observed in the poor autoregulatory group, in which coronary resistance averaged ~ 40 mmHg/mL/min/g, regardless of change in $CvPO_2$ (Fig. 7b).

Additional meta-analyses of data from the current and prior studies by our laboratory are presented in Fig. 8. These data provide a wide range of $CvPO_2$ values (from 13 to 45 mmHg) under diverse patho-physiologic perturbations (hemodilution [38], hypoxemia, catecholamine infusion, inhibition of Ca^{2+} channels [7]) and reveal significant relationships between coronary venous PO_2 and both autoregulatory Gc ($P < 0.001$; r = −0.753; Fig. 8a) and slope ($P < 0.001$; r = 0.526; Fig. 8b).

Discussion

The present study was designed to challenge the local metabolic hypothesis of coronary pressure-flow autoregulation. To examine the extent to which myocardial oxygen tension influences the degree of autoregulatory behavior, we performed a series of pressure-flow experiments in the absence and presence of hypoxemia ($PaO_2 < 40$ mmHg) with or without dobutamine to augment MVO_2. Hypoxemia was utilized to augment the proposed metabolic error signal ($CvPO_2$) while simultaneously attenuating underlying coronary vasomotor tone and thus, myogenic responsiveness [41, 44]. The primary novel findings of this investigation are that the degree of coronary vasodilation in response to hypoxemia is precisely sufficient to maintain myocardial oxygen delivery over a wide range of CPPs, without compromising the degree of autoregulatory behavior. Reductions in coronary vascular resistance in response to decreases in CPP between 120 to 60 mmHg predominantly occur below $CvPO_2$ values of ~ 25 mmHg. Taken together, these findings support the presence of an autoregulatory threshold under which highly sensitive oxygen-sensing pathway(s) act to preserve sufficient myocardial oxygen delivery as CPP is reduced during increases in MVO_2 and/or reductions in arterial oxygen content.

Hypoxemia and local metabolic coronary autoregulation

Initial support for a local metabolic mechanism of autoregulation is found in the observation that decreases in CPP are accompanied by progressive reductions in $CvPO_2$ (Fig. 1d and Fig. 4d). This result is consistent with prior studies [7, 35, 50, 54, 57] and reliably occurs irrespective

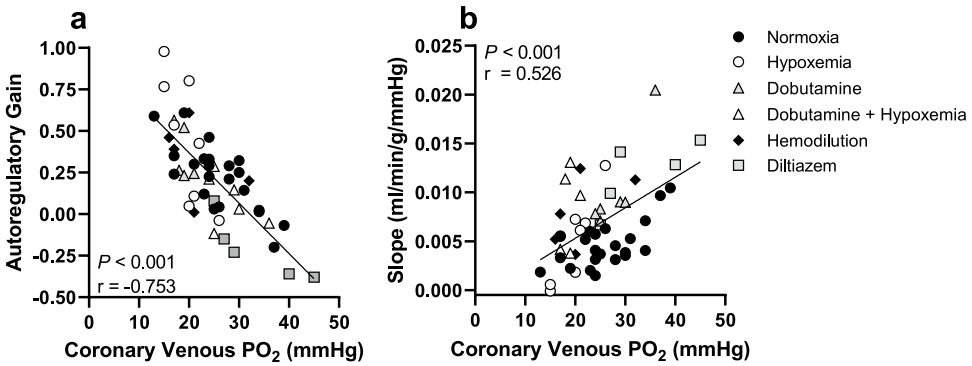

Fig. 8 Effects of Hypoxemia, Dobutamine ± Hypoxemia, and $CvPO_2$ on the Slope of the coronary pressure-flow relationship. Meta-analyses of data from our laboratory under various patho-physiologic perturbations (hemodilution [38], hypoxemia, dobutamine infusion, inhibition of $Ca.^{2+}$ channels [7]). **a** Strong inverse relationships between autoregulatory Gc (CPP 120 – 60 mmHg) and coronary venous PO_2 (taken at CPP = 100 mmHg). **b** Significant positive association between slope of the relationship between coronary blood flow and CPP (range 120 – 60 mmHg) and $CvPO_2$ (taken at CPP = 100 mmHg)

of underlying physiologic condition; even when coronary blood flow is entirely pressure-dependent when $Ca_V1.2$ channels are inhibited by diltiazem [7]. Thus, it is apparent that changes in $CvPO_2$ are a direct consequence of changes in CPP. However, the extent to which reductions in $CvPO_2$ represent changes in myocardial oxygenation and thus the postulated error signal for local metabolic feedback control remains controversial [13, 52] (see *Limitations of the study* below). Central to this argument is the understanding that conditions that produce coronary vasodilation, i.e., increases in $CvPO_2$, are associated with diminished autoregulatory responsiveness [19]. Interpretation of whether this impairment is related to a reduction of the metabolic error signal and/or attenuation of pressure-dependent myogenic reactivity has proven quite challenging.

The primary goal of the present study was to separate these confounding influences by examining coronary autoregulatory behavior (Gc and slope) in the same animals before and during systemic hypoxemia ± increases in MVO_2. Compelling evidence for local metabolic control is found in the coronary response to reductions in PaO_2 (< 40 mmHg), as the degree of coronary vasodilation achieved (Fig. 1a) exactly matched that required to maintain myocardial oxygen delivery (Fig. 1b) across CPPs ranging from 140 to 40 mmHg. Assessment of the degree of autoregulation under these conditions revealed somewhat paradoxical findings in that average Gc was significantly increased (Fig. 3a) while slope of the coronary flow vs. CPP relationship (Fig. 3c) remained unchanged. The reason for this discrepancy is mathematical as the Gc calculation involves normalization of relatively similar group changes in coronary flow to higher values of flow during hypoxemia. Closer examination of these data indicates the presence of responders and non-responders, which appears to be related, at least in part, to differences in underlying levels of $CvPO_2$ at CPP = 100 mmHg (Fig. 3b and d). These data are consistent with earlier studies that support the association of improvements in autoregulatory capability on lower (physiologic) levels of $CvPO_2$ [2, 19, 22]. These previous reports relied on administration of pharmacologic vasoconstrictor or vasodilator compounds and/or changes in heart rate to manipulate $CvPO_2$ [19, 22]. Importantly, such interventions would act to similarly modulate both metabolic and myogenic mechanisms in the same direction; e.g. vasodilator influence would reduce coronary resistance (diminish myogenic response [41, 44]) and increase $CvPO_2$ (diminish metabolic error signal [7]). Thus, utilization of hypoxemia in the present study is unique in that, reductions in PaO_2 represent a vasodilator influence that reduces coronary resistance, thereby lessening the myogenic response, yet also decreases $CvPO_2$ (increased metabolic error signal). Accordingly, our present findings implicate myocardial reliance on oxygen-sensitive, as opposed to pressure-dependent pathways to sustain myocardial oxygen delivery and the degree of pressure-flow autoregulation in the presence of marked hypoxic coronary vasodilation.

Similar tendencies in the ability of the coronary circulation to maintain myocardial oxygen delivery (Fig. 4b) and autoregulatory capability (Fig. 6c) were also noted as CPP was reduced during increases in MVO_2 and hypoxemia. While there is strong evidence to support that autoregulatory behavior occurs independent of underlying changes in MVO_2, (Fig. 6; [19, 22, 26, 45, 55]). recent findings of Kiel et al. indicate that autoregulation was attenuated by hemodilution (~ 50% reduction in hematocrit) and dobutamine-induced increases in MVO_2, despite physiologic values of $CvPO_2$ (averaged 26.4 ± 2.8 at CPP 100 mmHg) [38]. Based on the assumption that $CvPO_2$ reflects myocardial tissue oxygenation, this finding was interpreted to support a myogenic-based mechanism as reductions in Gc were related to diminished levels of vasomotor tone, independent of any underlying differences in $CvPO_2$. However, direct comparison of coronary response variables under these conditions reveal that coronary blood flow was ~ 90% higher and coronary resistance ~ 50% lower with hemodilution + dobutamine (relative to hypoxemia + dobutamine). Thus, the discrepant findings of the present study vs. that of Kiel et al. are most likely related to insufficient vasomotor reserve for autoregulation under the hemodilution + dobutamine condition (Fig. 7b).

Coronary vascular resistance and metabolic error signal

Central to the local metabolic hypothesis is the paradigm that reductions in coronary resistance are coupled with decreases in $CvPO_2$. This contention is directly supported by previous studies which demonstrate a tight, linear relationship between coronary resistance and coronary venous oxygen tension or content [19, 21, 22]. Results from this investigation expand these earlier observations and provide a more complete model of the complexities and interplay between these key variables. In particular, average data over CPPs ranging from 120 to 60 mmHg from each of the experimental conditions in this study indicate that coronary resistance remains relatively stable with changes in CPP until $CvPO_2$ falls below ~ 25 mmHg (Fig. 7a). The presence of a threshold oxygen tension for autoregulatory behavior is consistent with the seminal study of Dole and Nuno in 1986 [19], and is evident under normoxic-control conditions and during dobutamine administration where metabolic vasodilation has reduced coronary resistance by ~ 50%. The lack of change in coronary resistance indicates that neither a metabolic nor myogenic mechanism is operational at higher values of $CvPO_2$. However, if/when $CvPO_2$ falls below an apparent threshold, provoked by hypoxemic conditions in

this case, changes in coronary resistance in response to CPP become more pronounced. Incorporation of additional data from prior studies with strong autoregulatory gain (Gc = 0.99; [50]) vs. poor autoregulatory gain (Gc = −0.02; [38]) serve to further demonstrate that the slope of the relationship directly corresponds with the degree of autoregulatory behavior (Fig. 7b). Furthermore, examination of previous data from Kiel et al. [38] illustrate similar relationships between hemodilution and hypoxemic conditions as well as a "floor" to the relationship that becomes evident during hemodilution + dobutamine-induced increases in MVO_2; i.e., no change in resistance is provoked as $CvPO_2$ falls below the threshold value (Fig. 7b).

It is important to note that this interpretation adopts a simplified concept of coronary resistance as a single value computed as the average CPP divided by absolute coronary flow. In the beating heart in vivo, regional perfusion is dynamically matched to regional metabolism [3], with myocardial mechanical work serving as both the driver of coronary flow and determinant of metabolic energy requirements. Alternatively, outside the autoregulatory range, contractile function follows pressure-mediated reductions in coronary flow [34, 46, 47]. To this end, further evaluation of the maintenance of regional contractile function relative to respective regional (transmural) perfusion in response to changes in CPP, arterial oxygen content, and/or MVO_2 would serve to strengthen the present observations. Additional incorporation of phenomena observed here using multi-scale computational modeling [29, 36, 43] may also yield deeper insights than are immediately apparent from the data.

Limitations of the study

It is important to recognize that inherent to the examination of the local metabolic hypothesis is the assumption that $CvPO_2$ is a reliable estimate of myocardial tissue PO_2. While this assertion has been widely accepted and applied for many years [23, 27, 30], we acknowledge that measures of $CvPO_2$ may underestimate reductions in myocardial oxygenation, especially when MVO_2 (oxygen flux to the mitochondria) is elevated and/or when perfusion is compromised [13, 52]. Thus, the extent to which autoregulatory behavior relates to underlying $CvPO_2$ (Figs. 3 and 6) and/or $CvPO_2$ is associated with changes in MVO_2 (Figs. 2 and 5) should be interpreted with some degree of caution. Nevertheless, comprehensive meta-analysis of data from our current and prior studies, under a variety of (patho-)physiologic perturbations (hemodilution, hypoxemia, catecholamine infusion, inhibition of Ca^{2+} channels) supports that the degree of coronary pressure-flow autoregulation is related to underlying $CvPO_2$ (Fig. 8), as changes in coronary resistance in response to CPP are highest at values ≤ 20 mmHg (i.e. stronger autoregulation) and lowest at values > 25 mmHg (weak autoregulation; Fig. 7). To this end, it is important to recognize that the higher levels of $CvPO_2$ [6, 7, 24] observed in normoxic control swine in this study indicate a relative vasodilated state with higher degrees of myocardial oxygen extraction reserve (Tables 1 and 2), both of which negate the need for a robust autoregulatory response. We postulate that this relative weak degree of autoregulation is related to the anesthetized, extracorporeal perfusion preparation utilized to precisely control CPP in this study [8], as prior studies have demonstrated higher degrees of autoregulation in dogs [9], and humans [16]. We also hypothesize that observed reductions in MVO_2 to CPP (Figs. 1 and 4) are likely related to decreases in coronary vascular volume in hearts with poor autoregulation [2]. Nonetheless, the higher $CvPO_2$ and lower degree of autoregulation observed in normoxic control swine serendipitously afforded experimental conditions in which to directly examine the hypothesis that hypoxemia-induced reductions in $CvPO_2$ improve autoregulatory responsiveness.

Implications and conclusions

Data from of this investigation support that the degree of coronary vasodilation in response to hypoxemia is precisely sufficient to maintain myocardial oxygen delivery over a wide range of CPPs, without compromising the degree of pressure-flow autoregulation. Reductions in coronary vascular resistance in response to decreases in CPP (within autoregulatory range—120 to 60 mmHg) predominantly occur below an apparent $CvPO_2$ threshold value of ~ 25 mmHg, as long as adequate vasomotor reserve is present. The lack of change in coronary resistance above this limit indicates that myogenic and/or metabolic mechanisms remain largely inactive in hearts with higher levels of oxygen extraction reserve, similar to reported responses in right vs. left ventricular myocardium [58]. Given that myogenic responsiveness is attenuated as vasomotor tone is diminished [41, 44], our findings implicate myocardial reliance on highly sensitive oxygen sensing pathway(s) that act to preserve sufficient myocardial oxygen delivery as CPP is reduced during increases in MVO_2 and/or reductions in arterial oxygen content. Identification of specific metabolites and/or pathways responsible for such fundamental physiologic behavior remains elusive, as prior studies have failed to support a requisite role for numerous putative factors, including adenosine [20, 25, 32, 39], nitric oxide [48], $P2Y_1$ receptors [5], and/or end-effector K^+ channels [7, 25, 50].

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Author contributions CMW, JDT, and GMD conceived the study design. All authors contributed to the acquisition of presented data

and to the analysis and interpretation. CMW, JDT and GMD wrote the manuscript. All authors contributed to critical review and editing of the manuscript and approved the submitted version.

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Data availability The datasets generated and/or analyses performed in the present study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This manuscript does not contain clinical studies or patient data.

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