INTERPLAY BETWEEN METABOLIC AND MYOGENIC MECHANISMS IN CORONARY PRESSURE-FLOW AUTOREGULATION

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CHAPTER I: BACKGROUND AND LITERATURE

The myocardium requires continuous oxygen delivery to meet its metabolic demand under physiologic and/or pathologic conditions. Specifically, the heart relies on aerobic metabolism to supply >95% of the required ATP to sustain contractile function. At rest, the oxygen extraction of the left ventricle approaches ~80% (1, 2). Meaning, that not only does the left ventricle depend on oxygen delivery from the blood for metabolism, but also that any increase in metabolic need of the left ventricle must be met almost entirely by increasing flow. This characteristic high level of oxygen extraction is not only distinct from skeletal muscle, but also from the myocardium of the right ventricle. Both the right ventricle and skeletal muscle extract roughly 30-40% of the oxygen in the blood at rest, which provides a much greater oxygen extraction reserve to meet increases in metabolic demand (2-6). The dependence on oxygen delivery, near maximal oxygen extraction, and the never-ending workload of the left ventricle, creates a unique system where changes in key determinants of myocardial perfusion (e.g. pressure) must be matched by commensurate alterations in coronary vascular resistance (7).

Multiple mechanisms regulate the coronary circulation in order to maintain the delicate balance between myocardial oxygen delivery and metabolism. These factors include extravascular compressive forces and coronary perfusion pressure, as well as myogenic, local metabolic, endothelial, neural, and hormonal mechanisms (**Figure 1**). The existence of these mechanisms has been examined by numerous studies subjecting the coronary circulation to a variety of physiologic perturbations, including alterations in perfusion pressure, cardiac workload, and tissue oxygenation (1). I am particularly interested in mechanisms by which coronary blood flow is maintained relatively constant in the face of changing perfusion pressure (i.e., coronary pressure-flow autoregulation; **Figure 2**; (8-10)).

Coronary autoregulatory capability is critical under conditions such as coronary stenosis, where failure to ensure adequate oxygen delivery results in hypoperfusion and a rapid reduction in cardiac function (7, 11). Coronary autoregulation is important not only for keeping flow constant when pressure is reduced, but this mechanism also ensures stable flow when perfusion pressure increases. If coronary flow were not held relatively constant as coronary perfusion pressure increased, there would be increases in vascular volume, myocardial stiffness, and oxygen consumption (7, 12-14). Although the existence and critical nature of coronary autoregulation are well established, the mechanisms responsible for this phenomenon continue to be debated. While I recognize that many other aforementioned factors influence coronary blood flow (**Figure 1**), my goal is to further examine two mechanisms which are proposed to be responsible for coronary autoregulation: 1) local metabolic and/or 2) myogenic responses.

1) This local metabolic hypothesis suggests that a vasoactive end product of myocardial metabolism links coronary blood flow to cardiac work as pressure is reduced (1). For example, if perfusion pressure dropped while cardiac workload remained the same, the transient decrease in flow would cause an accumulation of vasodilatory metabolites. These metabolites reduce microvascular resistance and thereby act to restore flow to the original level. The appeal of the local metabolic hypothesis stems from studies demonstrating that coronary venous PO_2, a proposed index of myocardial tissue PO_2 (3), decreases with perfusion pressure and is directly associated with autoregulatory capacity (13, 15, 16). It has been documented that coronary autoregulation is only observed when $CvPO_2$ is below 25 mmHg, and abolished when $CvPO_2$ is over 32 mmHg (17). These findings support the contribution of a local metabolic mechanism to coronary pressure–flow autoregulation (17). Even so, efforts to identify specific metabolites or pathways of

autoregulatory behavior have yet to provide a consensus for any putative dilators such as adenosine (18-22) or nitric oxide (23).

2) There is potential for alternative intrinsic vasoactive mechanism to explain coronary autoregulatory behavior (1). Studies in isolated coronary arterioles have demonstrated the existence of a Bayliss (myogenic) response in which reduced intraluminal pressure stimulates vascular smooth muscle relaxation and *vice versa* (7, 24-27). The myogenic response is directionally consistent with autoregulatory capability, supported by mathematical studies (25, 28-30). However, studies to assess a causality are lacking. The contribution of a myogenic mechanism is also supported by studies showing that voltage-gated Ca^{2+} ($Ca_V1.2$) channels are critical for the coronary myogenic response (31), and that inhibition of $Ca_V1.2$ channels abolishes coronary pressure-flow autoregulation (13). However, $Ca_V1.2$ channels serve as an end-effector mechanism of both the myogenic and local metabolic pathways (see **Figure 3**).

The confounding nature of these competing influences that converge on a critical pathway is a major reason this phenomenon continues to be debated. Thus, in order to address this fundamental question, it is essential to develop techniques that attempt to separate the metabolic error signal from underlying myogenic influences and vice versa. My lab recently attempted to separate these mechanisms by using hemodilution (reduces coronary tone without altering $CvPO_2$) with and without dobutamine (augments metabolism and coronary blood flow) (32). This study by Kiel et al. supports that the local metabolic hypothesis is not sufficient to explain autoregulatory behavior as autoregulation was essentially absent in the presence of hemodilution and dobutamine, despite relatively unchanged (normal) values of coronary venous PO_2 (**Figure 4**). Another interesting finding from this study is the existence of a potential threshold zero-flow pressure (Pzf), which has been shown to be determined by overall vascular smooth muscle tone (18, 33-35), value after

which autoregulatory capability quickly falls. (**Figure 5**) These findings indicate that autoregulation could be more myogenic in origin. However, a role for local metabolic mechanism could still not completely ruled out (32).

In order to further examine the metabolic vs. myogenic mechanism of coronary pressure flow autoregulation, I proposed using hypoxemia, which unlike hemodilution results in coronary vasodilation and substantial reductions in coronary venous PO_2 ($CvPO_2$) (**Figure 6**) (12). Therefore, utilization of hypoxemic conditions would augment the underlying proposed metabolic error signal (↓ $CvPO_2$) yet diminish overall myogenic/vasomotor tone. Thus, if autoregulation were to increase during hypoxemia it will stand to bolster the local metabolic hypothesis considering autoregulation has overcome the decreased myogenic tone.

CHAPTER II

SPECIFIC AIMS

Define the extent to which exaggeration of the metabolic error signal with diminished levels of coronary tone influences coronary autoregulatory capability. Experiments utilize hypoxemia, which reduces tissue oxygenation ($CvPO_2$) and myogenic tone (Pzf) (1, 12, 36), as a tool to determine the degree to which metabolic signals and/or myogenic tone influence pressure-flow autoregulation. The working hypothesis is that if a local metabolic mechanism predominates, then autoregulatory capability will be directly related to the degree to which hypoxemia lowers $CvPO_2$, irrespective of reductions in coronary vasomotor tone. Conversely, if a myogenic mechanism predominates, then autoregulatory capability will be directly related to the degree to which hypoxemia reduces tone (Pzf), regardless of underlying $CvPO_2$. Association between augmented coronary autoregulatory capacity and lowered $CvPO_2$, along with a requisite threshold value of coronary Pzf, would support an interplay between metabolic and myogenic mechanisms.

SIGNIFICANCE AND INNOVATION

These studies utilize a unique, innovative, and translationally-relevant combination of state-of-the-art cardiovascular approaches to provide mechanistic insight into the regulation of coronary blood flow. This research is significant because understanding how metabolic and myogenic mechanisms contribute to coronary autoregulation may improve the diagnosis, treatment, and prevention of coronary flow impairments, which contribute to 1.5M myocardial infarctions per year in the US (37). The findings could benefit patients with coronary occlusions as well those with ischemia and no obstructive coronary artery disease (INOCA) by revealing new therapeutic strategies to treat myocardial ischemia (38). Basic, theoretical, and clinical significance to be gathered here includes: 1) a direct basic science comparison of 2 theoretically-based mechanisms of autoregulation; 2) establishing the quantitative contribution of metabolic and myogenic mechanisms to autoregulation; and 3) developing and testing of a new integrated paradigm for coronary autoregulation.

MATERIALS AND METHODS

Research Design: In an attempt to disentangle the roles, if any, of the local metabolic hypothesis and myogenic response involved in coronary autoregulation, I made measurements under normoxic and hypoxic conditions in swine. This was done while controlling perfusion pressure in the left anterior descending (LAD) coronary artery via a servo-controlled roller pump system. Coronary blood flow was continuously measured as perfusion pressure was reduced from 140 to 40 mmHg in 10 mmHg increments. Coronary zero-flow pressure (Pzf), an index of underlying myogenic tone (34, 35), was determined at perfusion pressures of 140, 120, 100, 80, 60, and 40 mmHg (discussion and interpretation below).

Samples of arterial and coronary venous blood were drawn at the same 20 mmHg pressure intervals and measurements of blood gas and oxygen content obtained. These values were used to calculate myocardial oxygen delivery and myocardial oxygen consumption (MVO_2). In order to facilitate comparison between animals, coronary blood flow was normalized to estimated mass of the perfusion territory as previously described by Feigl (3). Coronary vascular resistance (mmHg/ml/min/g) was calculated from measured coronary pressure and flow and was used to estimate the effective autoregulatory range (**Figure 2**). Closed loop autoregulatory gain (Gc) was calculated as described in **Equation 1** below (13, 14, 39) where ΔF is the change in coronary blood flow, and F is the coronary flow measured at given perfusion pressure (P). A Gc value of 1 reflects perfect autoregulation and values < 0 indicate no autoregulation.

$$Gc = 1 - ((\Delta F/F)/ (\Delta P/P)) \qquad \text{Eq. 1}$$

Methodology: 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). Eight Adult ~ 50 kg domestic swine (n = 3 male) were sedated with Telazol, xylazine, and ketamine (5.0, 2.5, and 2.5 mg/kg im, respectively) prior to anesthesia with buprenorphine (0.03 mg/kg im) and intravenous α-chloralose (60 mg/kg).

Anesthetized swine were intubated and ventilated with O_2-supplemented room air to achieve >95% oxyhemoglobin saturation and an end tidal CO_2 of ~40mmHg; as 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 provides continuous measurement of systemic blood pressure and heart rate, the venous catheter allows for administration of drugs (e.g. supplemental α-chloralose and heparin). The other femoral artery catheter supplies blood to an extracorporeal servo-controlled pump used to perfuse the LAD coronary artery at designated perfusion pressures, as previously described by our laboratory (13).

Succinylcholine (0.5 mg/kg iv) was administered, and then a thoracotomy in the left 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 was regulated by a servo-controlled roller pump and coronary blood flow was continuously measured by an in-line Transonic Systems flow transducer. The anterior interventricular vein was catheterized to allow for sampling of venous blood from the LAD perfusion territory. Following a ~15 min stabilization period, data was continuously recorded on IOX data acquisition software (EMKA Technologies).

Following surgical instrumentation, the normoxic (control) experimental protocol began. The servo-controlled roller pump was initially set to a perfusion pressure of 140 mmHg. Coronary perfusion pressure was checked via a Millar pressure transducer advanced through a Tuohy Borst Y connector into the servo perfusion line to ensure accuracy of the servo controller. Swine were allowed time to obtain a new steady at this perfusion pressure, as judged by stability of coronary flow. After steady state was achieved the data time point was marked and hemodynamic values recorded (systolic, diastolic and, mean blood pressures, heart rate, CPP, and coronary flow), as well as obtaining coronary venous and arterial blood samples.

Coronary Pzf, the pressure when coronary flow has ceased, which is predominantly determined by overall vascular smooth muscle tone (18, 33-35), was measured by clamping the extracorporeal coronary perfusion circuit for ~8s. Once blood flow returns to pre-Pzf values, servo-controlled pressure was lowered by 10 mmHg. Once a new steady state had been achieved, servo-controlled pressures were reduced in 10mmHg increments from an initial pressure of 140 mmHg down to a pressure of 40 mmHg. Blood sampling and Pzf data were obtained every 20 mmHg drop in perfusion pressure, while hemodynamic values were recorded every 10 mmHg drop.

Upon reaching 40 mmHg under normoxic conditions, the servo-controller was returned to 140 mmHg and again flow was allowed to come to a new steady state. After a steady state was achieved, nitrogen gas was continuously bled into the ventilation line in order to reduce the partial pressure of oxygen and achieve a stable level of hypoxemia (~50% oxyhemoglobin saturation). Once steady state of flow and SpO_2 were achieved, the protocol was repeated as described above.

Statistical analysis

Data are presented as mean ± SE. Statistical comparisons for data presented in **Table 1** 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. Pearson correlation analysis was utilized to assess the relationship between coronary resistance, changes in coronary blood flow, and autoregulatory gain relative to coronary venous PO_2 and Pzf. Lines of best fit are shown for significant associations with correlation coefficients ($r) > 0.40$. Gc between groups was compared with paired t-test. Statistical analyses were performed with GraphPad Prism 9.2.0 software (GraphPad Software, San Diego, California USA).

RESULTS

Hemodynamic and coronary responses to alterations in perfusion pressure

Hemodynamic and coronary responses to graded reductions in CPP for each of the treatment groups are provided in **Table 1**. Reducing oxyhemoglobin saturation from ~100% (control) to ~50% (hypoxemia) increased coronary blood flow ($P < 0.001$), heart rate ($P = 0.003$), hematocrit ($P = 0.006$), and MVO_2 ($P = 0.030$), while decreasing mean arterial pressure ($P < 0.001$), but did not significantly affect oxygen delivery ($P = 0.140$)

Effects of hypoxemia induced changes on coronary blood flow and resistance as CPP was reduced from 140 to 40 mmHg are shown in **Figure 7**. Over the autoregulatory range of CPP (120 to 60 mmHg), the slope of the relationship between coronary blood flow and CPP equaled 0.0046 mL/min/g/mmHg (**Figure 7A)** and autoregulatory gain averaged 0.18 ± 0.05 (**Figure 7B**). Significant reductions in coronary resistance (~ 50% relative to control) produced by hypoxemia resulted in a modest decrease in the slope of the coronary flow vs. CPP relationship (0.0062 mL/min/g/mmHg; $P = 0.156$), and significantly increased autoregulatory gain (0.45 ± 0.14; $P = 0.017$). Time control experiments ($n = 3$) were also performed and showed no difference in slope of the relationship between coronary blood flow and CPP between the first control run and repeated control run **(Figure 8**; $P = 0.237$)

Coronary Pzf, vascular smooth muscle tone, and autoregulatory capability

Representative tracings to demonstrate how coronary Pzf was determined at CPPs of 120 and 60 mmHg are provided in **Figure 9**. Occlusion of the coronary perfusion circuit resulted in a rapid reduction in coronary blood flow and stabilization of coronary pressure at zero flow within ~ 6 s

of the occlusion. Consistent with previous studies in the literature (18, 33-35, 40, 41), coronary Pzf was related with underlying coronary vascular tone as Pzf decreased from 13.0 ± 2 mmHg at CPP = 100 mmHg in control swine, and to 10 ± 1 mmHg following hypoxemia (P = 0.049), (Table 1). Coronary Pzf also decreased ~ 60% as CPP was lowered from 140 to 40 mmHg in each of the treatment groups (P < 0.001). Pzf was related to overall coronary vascular resistance (r = 0.79; P < 0.001) (**Figure 10A**), but coronary Pzf was negatively correlated with autoregulatory gain (r = -0.51; P = 0.006) (**Figure 10B**).

Effects of coronary venous PO_2 on coronary pressure-flow autoregulation

Under normoxic conditions, coronary venous PO_2 decreased as CPP was lowered from 140 to 40 mmHg (33 ± 1 to 20 ± 1 mmHg). Hypoxemia caused a significant reduction in the relationship between $CvPO_2$ and CPP (22 ± 1 to 14 ± 1 mmHg; P < 0.001) (**Table 1**). Regression analysis revealed that reductions in coronary resistance produced by hypoxemia were predicted by underlying decreases in coronary venous PO_2 (**Figure 11A**). To assess the relationship between coronary venous PO_2 and autoregulatory capacity, changes in autoregulatory gain (20 mmHg increments from CPP 120–60 mmHg) were plotted relative to their respective coronary venous PO_2. Pearson correlation analyses determined that changes in autoregulatory gain (**Figure 11B**; P < 0.001) were significantly related to coronary venous PO_2.

DISCUSSION

Going back over 60 years, studies have demonstrated an innate ability of the coronary circulation to maintain adequate myocardial perfusion over a wide range of driving pressures; however, the mechanisms responsible for this pressure-flow autoregulation are still debated (1, 10, 42). Two mechanisms dominate the current discussion, a local metabolic hypothesis (myocardial oxygen tension) and underlying intrinsic changes in vasomotor tone (myogenic response). In order to further examine the mechanism, and/or potential interplay between these two pathways, we performed autoregulatory experiments (CPPs ranging from 140 to 40 mmHg) in the absence and presence of hypoxemia (~ 50% reduction in oxygen saturation). Hypoxemia was utilized in order to augment the metabolic signal while simultaneously attenuating the myogenic response which has been shown to occur via reductions in underlying coronary tone (31, 43). Findings from the present studies support the hypothesis that coronary autoregulatory behavior is augmented by exaggeration of the proposed metabolic error signal, independent of reductions in underlying tone.

Autoregulatory capability and metabolic control

The metabolic hypothesis of coronary autoregulation relies on the observation that as CPP decreases coronary venous PO_2 decreases, as well as seen in this study (**Table 1**) and prior studies (13, 15, 16, 39, 44). Under this hypothesis, the reduction in CPP leads to decreasing coronary venous PO_2 and further the production of vasodilatory metabolites in proportion to these pressure-dependent reductions in tissue oxygenation, resulting in the observed autoregulatory behavior. Data from the present study stand to bolster the metabolic hypothesis, as not only was autoregulatory gain significantly increased under hypoxemic conditions, but the

degree to which gain increased strongly correlated with the degree to which hypoxemia lowered coronary venous PO_2 (**Figure 7B; Figure 11B)**.

Autoregulatory capability and Pzf

In order to analyze the effect of coronary vasomotor tone (myogenic response) on autoregulatory behavior, I utilized coronary Pzf measurements at 20 mmHg increments across all treatment groups. The concept that zero-flow pressure is predominantly determined by underlying vascular smooth muscle tone has been established by numerous earlier studies (18, 33-35, 40, 41). Pzf was determined in the present study by stopping/clamping the extracorporeal coronary perfusion circuit for ~ 8 s while the heart continued to beat. Pzf obtained via this method relates to the decay of pressure as a function of resistance and capacitance of the system. When discussing and comparing coronary Pzf between studies it is important to appreciate the variety of methods that have been utilized, which may yield differing values different methods may obtain. Prior studies have employed vagal stimulation (long diastole), decreasing aortic or extracorporeal reservoir pressure, AV node ablation and pacing, and/or occlusion of perfusion circuit in both beating and non-beating hearts (17, 34, 45-51). Although the values of coronary Pzf may differ between these methods, comparison of Pzf within and between the current and previous studies confirms that Pzf varies linearly with CPP and coronary vascular tone (**Table 1**); i.e., Pzf was reduced by hypoxemia at a given CPP as well as diminished by reductions in CPP across all treatment groups. While interpretation of coronary Pzf has been controversial (33, 40), there is strong evidence that measurements of Pzf serve as a reliable index of underlying coronary vascular tone, as coronary Pzf was directly related to coronary vascular resistance across all treatment groups in this study (**Figure 10a**)

Although my lab recently concluded that autoregulatory behavior is primarily controlled via a myogenic response (32), the findings from this investigation directly challenge that conclusion. In the present study, Pzf (vasomotor tone) was inversely related to autoregulatory gain (**Figure 10b**). That is, as underlying coronary vascular tone decreased with hypoxemia, autoregulatory capability increased, the opposite of what a myogenic mechanism to coronary pressure-flow autoregulation would predict.

Future directions

The data presented are seemingly incompatible with our recent studies using hemodilution and dobutamine (32), which were interpreted to mean that coronary autoregulation relies on underlying tone, without dependence on oxygen tension. To further examine the incongruity, I propose experiments using dobutamine to increase MVO_2 in the absence and presence of hypoxemia to reduce coronary venous PO_2. I predict that dobutamine will abolish autoregulation, and that the combination of dobutamine plus hypoxemia will restore autoregulation. The rationale is that if underlying myogenic tone predominates, then the results would reflect those obtained from hemodilution and dobutamine, i.e., a loss of autoregulatory capability. In contrast, if autoregulatory capability increases with hypoxemia then it serves to further bolster the local metabolic hypothesis of coronary autoregulation.

Limitations

We acknowledge that cannulation and pump perfusion of coronary circulation may impact overall autoregulatory capability (52). However, this approach is required to obtain the tightly controlled pressures and measurements proposed in this investigation.

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Coronary Perfusion Pressure (mmHg)	140	120	100	80	60	40	CPP	Condition	Interaction
Mean Arterial Pressure (mmHg)									
Control	99 ± 6	99 ± 5	97 ± 5	96 ± 5	95 ± 5	94 ± 5	P =.026	P < .001	P = .613
Hypoxemia	77 ± 6	73 ± 6	72 ± 6	72 ± 5	72 ± 5	70 ± 4			
Heart Rate (Beats/Min)									
Control	86 ± 7	86 ± 7	89 ± 7	89 ± 7	91 ± 9	91 ± 8	P = .083	P = .003	P = .252
Hypoxemia	111 ± 7	112 ± 7	114 ± 8	115 ± 9	121 ± 10	125 ± 11			
Hematocrit %									
Control	30 ± 1.0	29 ± 0.5	29 ± 0.4	29 ± 0.4	29 ± 0.8	29 ± 0.4	P = .254	P = .006	P = .084
Hypoxemia	31 ± 0.8	31 ± 0.7	32 ± 0.9	32 ± 0.9	33 ± 1.1	33 ± 1.0			
Coronary Blood Flow (mL/min/g)									
Control	0.81 ± 0.09	0.67 ± 0.07	0.54 ± 0.06	0.46 ± 0.05	0.40 ± 0.04	0.35 ± 0.04	P < .001	P < .001	P = .058
Hypoxemia	1.32 ± 0.09	1.22 ± 0.08	1.08 ± 0.09	0.99 ± 0.12	0.90 ± 0.11	0.67 ± 0.07			

Coronary Perfusion Pressure (mmHg)	**140**	**120**	**100**	**80**	**60**	**40**	**CPP**	**Condition**	**Interaction**
MVO_2 (µL O_2/min/g)									
Control	56 ± 7	52 ± 6	49 ± 6	48 ± 5	46 ± 6	41 ± 5	P < .001	P = .030	P = .219
Hypoxemia	66 ± 6	63 ± 5	62 ± 6	59 ± 6	58 ± 7	46 ± 5			
O_2 Delivery (µL O_2/min/g)									
Control	118 ± 13	99 ± 11	80 ± 9	68 ± 8	59 ± 7	51 ± 6	P < .001	P = .140	P = .039
Hypoxemia	116 ± 8	105 ± 6	92 ± 6	82 ± 8	73 ± 8	56 ± 6			
Coronary Venous PO_2 (mmHg)									
Control	33 ± 1	31 ± 2	27 ± 2	23 ± 1	21 ± 1	20 ± 1	P < .001	P < .001	P < .001
Hypoxemia	22 ± 1	21 ± 1	20 ± 1	18 ± 1	16 ± 1	14 ± 1			
Pzf (mmHg)									
Control	17 ± 3	13 ± 1	13 ± 2	11 ± 2	10 ± 2	6 ± 1	P < .001	P = .049	P = .207
Hypoxemia	12 ± 1	10 ± 1	10 ± 1	8 ± 1	7 ± 1	5 ± 1			

Table 1 Hemodynamic and coronary responses to graded changes in perfusion pressure

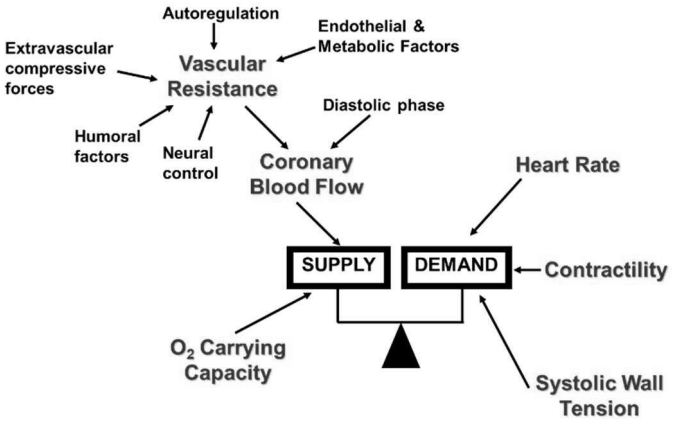

Figure 1. Schematic diagram of the multiple mechanisms involved in regulating the coronary circulation From Goodwill et al. 2017

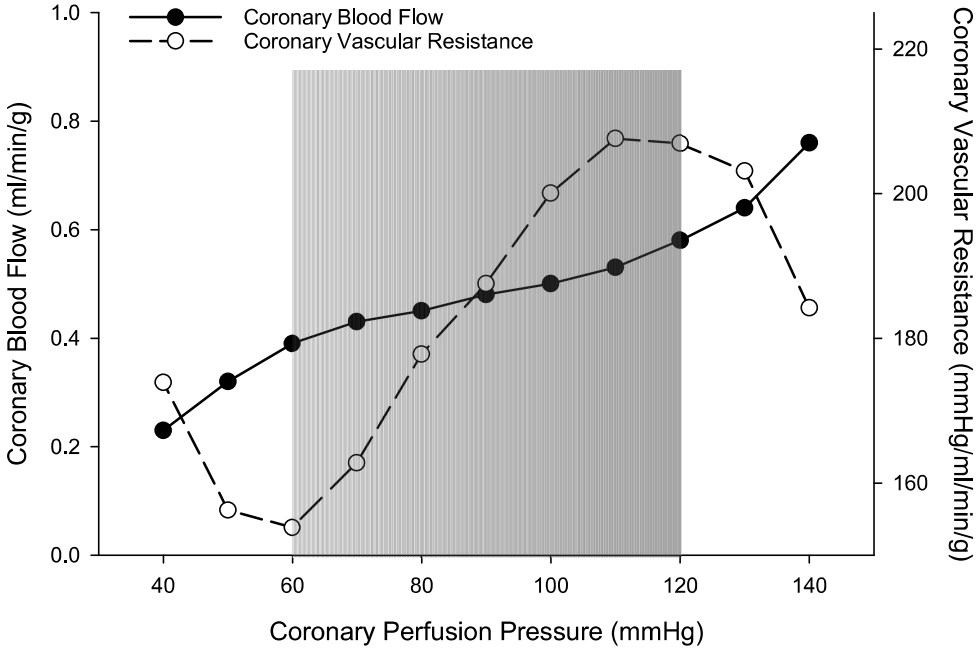

Figure 2. Relationship between coronary blood flow and coronary vascular resistance relative to coronary perfusion pressure. Closed circles denoting coronary blood flow and open circles coronary vascular resistance. Green rectangle denoting range of autoregulation. From Goodwill et al. 2017

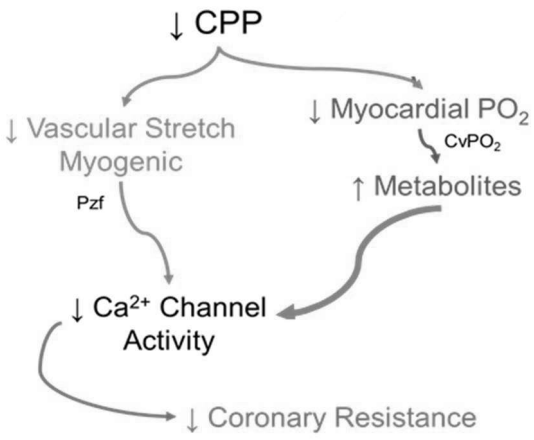

Figure 3. Schematic diagram of proposed mechanisms of coronary autoregulation

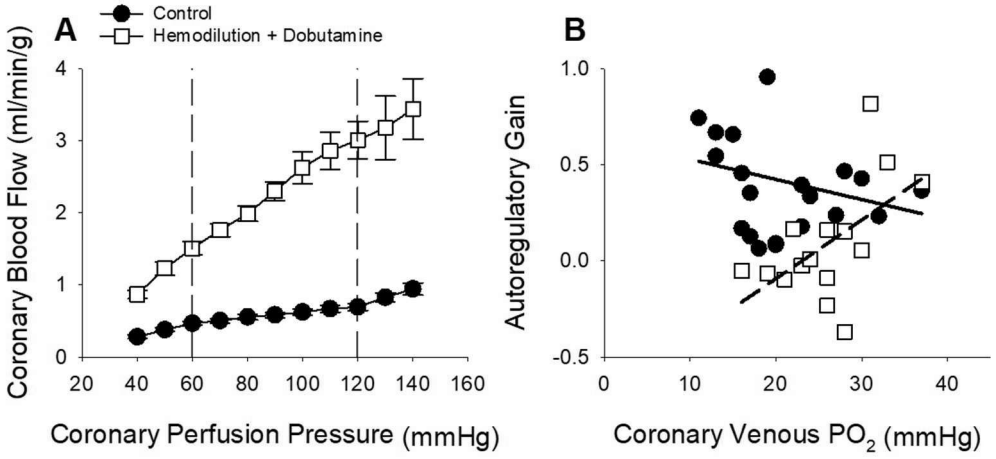

Figure 4. Relationships between coronary blood flow vs. CPP (**A**) and autoregulatory gain vs. $CvPO_2$ (**B**). Autoregulatory gain calculated as changes in coronary flow over 20mmHg increments at pressures ranging from 120 to 60 mmHg relative to coronary venous PO_2. Responses are plotted in the absence (solid line) and presence of euvolemic hemodilution (dashed line) (~50% reduction in hematocrit) plus dobutamine (increase heart rate ~75-100% above baseline levels). Data from Kiel et al. 2018.

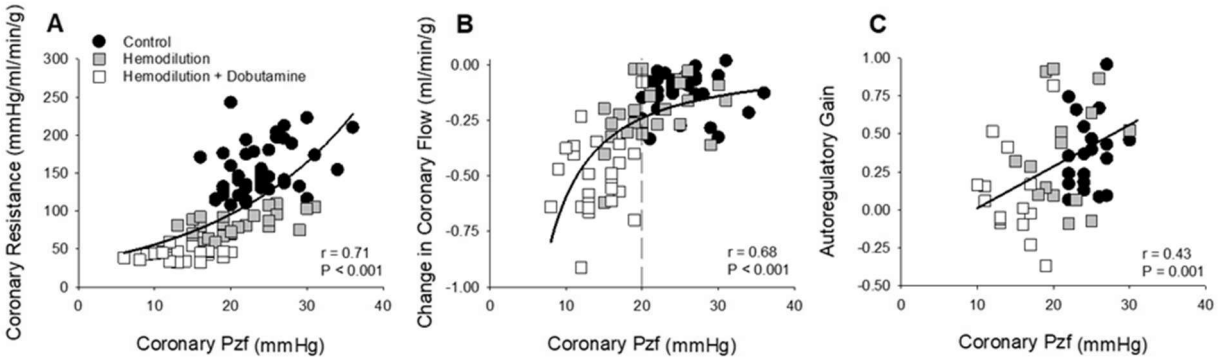

Figure 5. Previous study from this lab investigating autoregulatory mechanisms. Relationship between coronary zero-flow pressure (Pzf) and coronary autoregulatory capacity. Coronary Pzf was closely related to coronary vascular resistance as CPP was lowered from 140 to 40 mmHg in all groups: control (n = 7); hemodilution (n = 6); hemodilution + dobutamine (n = 5) (**A**) Changes in coronary blood flow (20 mmHg increments) remained modest at Pzf > 20 mmHg and significantly decreased below this threshold value (**B**). Autoregulatory gain (CPP ranging from 120 to 60 mmHg) was positively correlated with coronary Pzf (**C**). Data from Kiel et al. 2018.

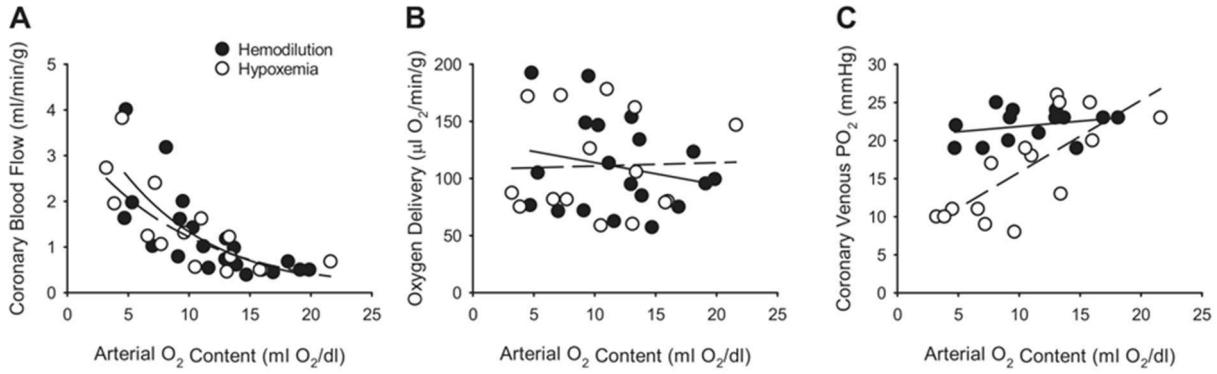

Figure 6. Differences between hypoxemia and hemodilution in autoregulatory control. Relationship between coronary blood flow (**A**), myocardial oxygen delivery (**B**), coronary venous PO2 (**C**) relative to arterial oxygen content in response to hemodilution (solid line) and hypoxemia (dashed line). Arterial oxygen content was used to normalize the level of oxygen deficit in each study. Data from Tune et al. 2020.

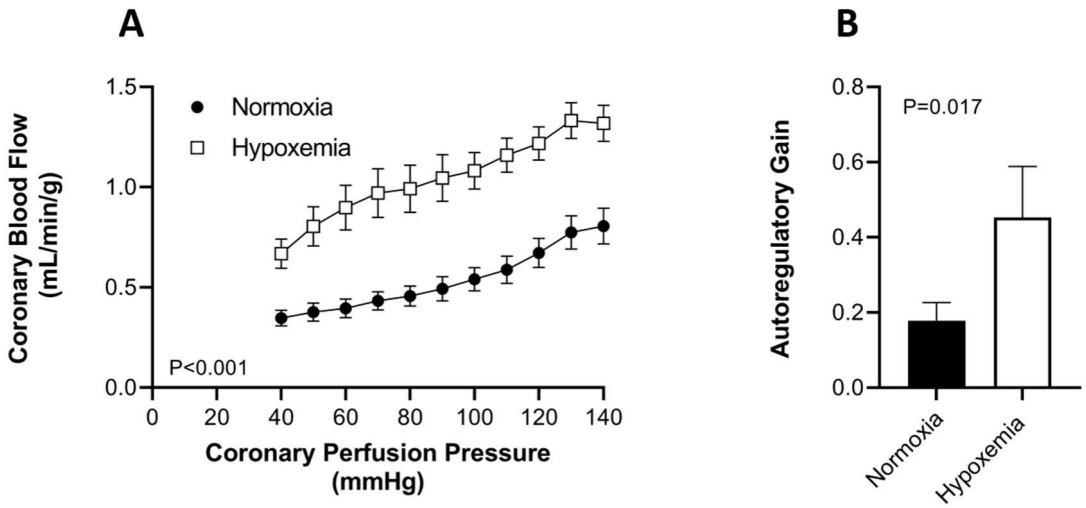

Figure 7. Effects of alterations in oxygen saturation on coronary pressure–flow autoregulation. Coronary blood flow increased at a given CPP under hypoxemic conditions. Relative to normoxic swine, the slope of flow-pressure relationship within the autoregulatory range (CPP 120-60 mmHg) was only modestly decreased by hypoxemia (**A**; P=0.156), but significantly increased autoregulatory gain (**B**; P=0.017).

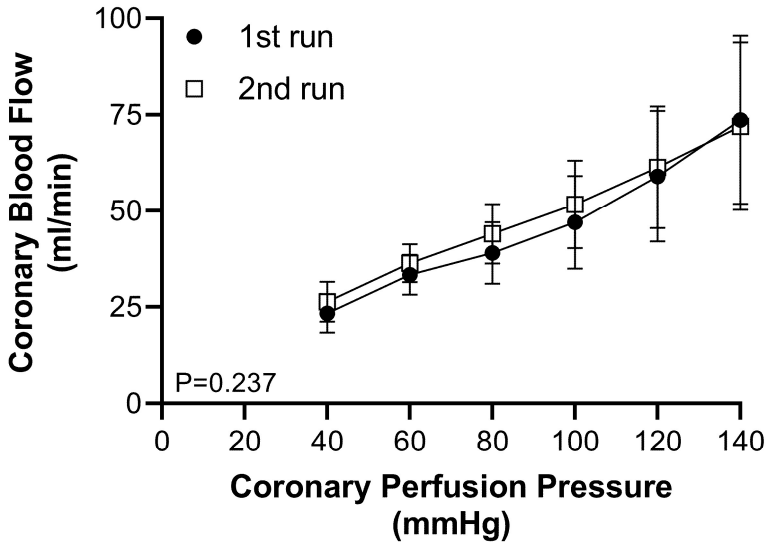

Figure 8 Coronary autoregulation time-controls. Coronary pressure-flow autoregulation is unchanged between back-to-back CPP runs (P=0.237).

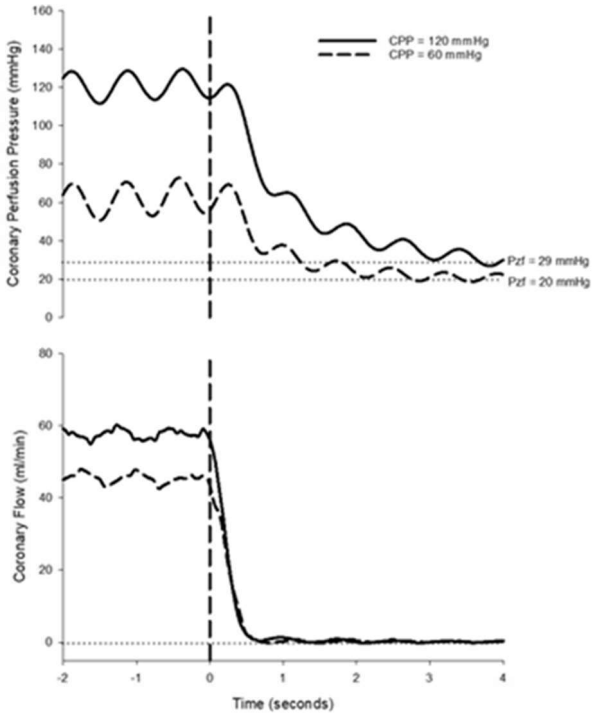

Figure 9 Representative tracings of coronary perfusion pressure and blood flow over time before and during a 4 s coronary artery occlusion to determine coronary zero-flow pressure (Pzf).

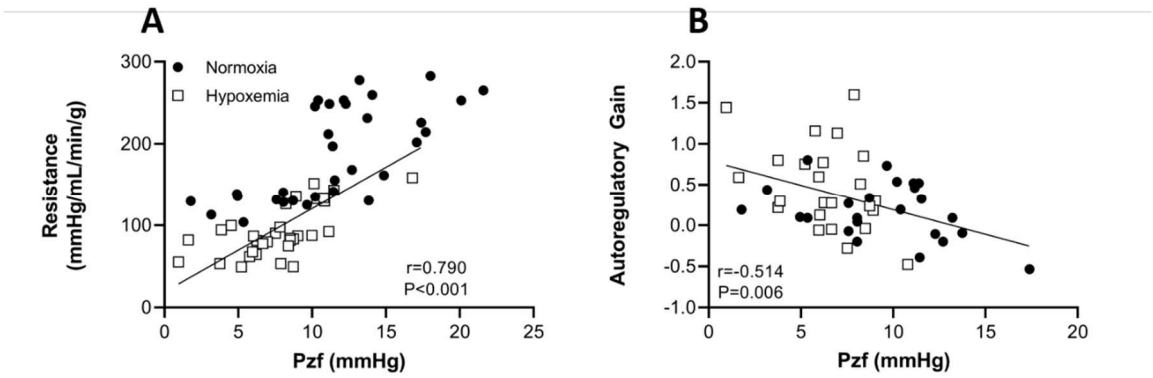

Figure 10 Relationship between Pzf and coronary autoregulatory capacity. Coronary Pzf was closely related to coronary vascular resistance as CPP was lowered from 140 to 40 mmHg in all groups (**A**). Autoregulatory gain (CPP ranging from 120 to 60 mmHg) was negatively correlated with coronary Pzf (**B**).

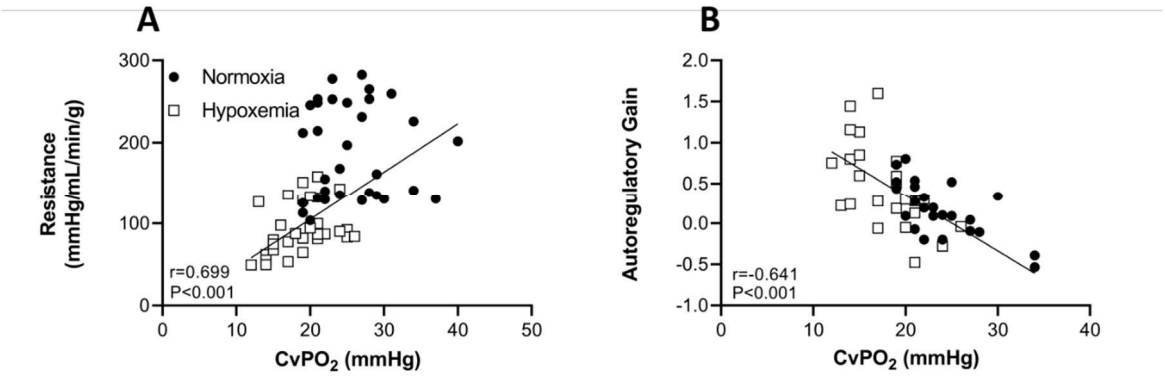

Figure 11 Relationship between coronary venous PO_2 and coronary autoregulatory capacity. Coronary venous PO_2 was closely related to coronary vascular resistance as CPP was lowered from 140 to 40 mmHg in all groups (**A**). Autoregulatory gain (CPP ranging from 120 to 60 mmHg) was negatively correlated with coronary venous PO_2