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Local metabolic hypothesis is not sufficient to explain coronary autoregulatory behavior

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Abstract

The local metabolic hypothesis proposes that myocardial oxygen tension determines the degree of autoregulation by increasing the production of vasodilator metabolites as perfusion pressure is reduced. Thus, normal physiologic levels of coronary venous PO_2, an index of myocardial oxygenation, are proposed to be required for effective autoregulation. The present study challenged this hypothesis through determination of coronary responses to changes in coronary perfusion pressure (CPP 140–40 mmHg) in open-chest swine in the absence ($n = 7$) and presence of euvolemic hemodilution (~ 50% reduction in hematocrit), with ($n = 5$) and without ($n = 6$) infusion of dobutamine to augment MVO_2. Coronary venous PO_2 decreased over similar ranges (~ 28–15 mmHg) as CPP was lowered from 140 to 40 mmHg in each of the groups. However, coronary venous PO_2 was not associated with changes in coronary blood flow ($r = -0.11$; $P = 0.29$) or autoregulatory gain ($r = -0.29$; $P = 0.12$). Coronary zero-flow pressure (Pzf) was measured in 20 mmHg increments and determined to be directly related to vascular resistance ($r = 0.71$; $P < 0.001$). Further analysis demonstrated that changes in coronary blood flow remained minimal at Pzf > 20 mmHg, but progressively increased as Pzf decreased below this threshold value ($r = 0.68$; $P < 0.001$). Coronary Pzf was also positively correlated with autoregulatory gain ($r = 0.43$; $P = 0.001$). These findings support that coronary autoregulatory behavior is predominantly dependent on an adequate degree of underlying vasomotor tone, independent of normal myocardial oxygen tension.

Keywords

Coronary; Autoregulation; Zero-flow pressure; Swine

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Compliance with ethical standards

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

Introduction

The coronary circulation is actively regulated by a variety of mechanisms to maintain an adequate balance between myocardial oxygen delivery and metabolism. This point is demonstrated by the coronary response to a variety of physiologic perturbations, including alterations in perfusion pressure, cardiac workload, and tissue oxygenation [24]. Studies dating back to the 1950s definitively established that the coronary circulation has the innate ability to maintain relatively constant blood flow over a wide range of perfusion pressures [1] and that the overall level of this pressure–flow autoregulation adjusts to myocardial oxygen consumption (MVO_2) [1, 22, 38]. The autoregulatory capacity of the coronary circulation is particularly important to compensate for intermediate degrees of stenosis (distal coronary pressures ≥ 60 mmHg) where, if absent, hypoperfusion can result in rapid reductions in cardiac function and/or myocardial injury [21, 24]. Despite the critical nature of coronary autoregulation, the mechanisms responsible for this physiologic phenomenon continue to be debated.

One of the most prominent theories to explain coronary pressure–flow autoregulation focuses on metabolic regulation of coronary microvascular resistance. The local metabolic hypothesis proposes that myocardial oxygen tension determines the degree of autoregulation by increasing the production of vasodilator metabolites as perfusion pressure is reduced [16, 22, 24]. This paradigm is supported by studies which have demonstrated that coronary venous PO_2, a commonly used index of myocardial tissue PO_2 [22], decreases with perfusion pressure [3, 8, 26, 42, 45] and that the overall autoregulatory capacity (i.e., gain) is directly dependent on normal physiologic levels of coronary venous PO_2 [16]. Dole and Nuno documented that coronary autoregulation is only observed when coronary venous PO_2 is below 25 mmHg and abolished when oxygen tension exceeds 32 mmHg. As such, local metabolic control is purported to be the dominant mechanism of coronary pressure–flow autoregulation [16]. However, efforts to elucidate specific metabolites or pathways that contribute to autoregulatory behavior have failed to show any role for putative dilators such as adenosine [17, 19, 25, 31], nitric oxide [40], and/or end-effector K^+ channels [8, 19, 42].

Despite the attractiveness of the metabolic hypothesis of coronary autoregulation, interpretation of the inverse relationship between autoregulatory gain and coronary venous PO_2 is confounded by effects of other vasoactive mechanisms, primarily the vascular smooth muscle response to alterations in intraluminal pressure [4]. Definitive evidence of the myogenic (Bayliss) response in the coronary circulation comes from studies which demonstrate pressure-dependent changes in the diameter of isolated pressurized coronary arterioles [33–35, 37]. Importantly, additional experiments also established that the overall degree of this intrinsic myogenic response decreases as underlying vasomotor tone is reduced [34, 37]. These findings have critical implications for prior in vivo observations in that increases in coronary venous PO_2, typically induced by the administration of vasodilator agents (e.g., adenosine) and/or reductions in key determinants of MVO_2 (e.g., heart rate) [3, 5, 8, 14, 16], would be predicted to diminish coronary autoregulatory capacity not via local metabolic pathways per se, but through the attenuation of a pressure-dependent myogenic mechanism. This contention is corroborated by earlier studies which documented that voltage-gated Ca^{2+} ($Ca_V1.2$) channels are critical for the coronary myogenic response [37]

and that inhibition of $Ca_V1.2$ channels abolishes coronary autoregulation in vivo [8]. Accordingly, there is ample evidence to support the alternative hypothesis that autoregulation in the coronary circulation is predominantly myogenic in origin and thus more dependent on an adequate degree (threshold) of underlying coronary vasomotor tone rather than the prevailing level of myocardial oxygen tension.

The purpose of this investigation was to examine the metabolic hypothesis of coronary autoregulation through alterations in the overall vasomotor tone and/or MVO_2, independent of the underlying differences in coronary venous PO_2. Experiments were designed to determine the coronary responses to changes in perfusion pressure (140–40 mmHg) in the absence and presence of euvolemic hemodilution (~ 50% reduction in hematocrit), with and without infusion of dobutamine to augment MVO_2. Hemodilution was utilized in these studies as reductions in hematocrit are well known to increase coronary blood flow and diminish vasodilator reserve with little/no change in coronary venous PO_2 [11, 28, 36]. The effects of these conditions on coronary vasomotor tone were assessed through measurements of coronary pressure when coronary flow had ceased [i.e., zero-flow pressure (Pzf)] [5]; which has been shown to be predominantly determined by overall vascular smooth muscle tone [14, 15, 17, 30, 41, 47]. Data from these experiments offer novel insight into the fundamental question regarding the dominant mechanism(s) of coronary pressure–flow autoregulation.

Methods

This investigation was approved by the Indiana University School of Medicine 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). Adult ~ 50 kg male domestic swine were sedated with Telazol, xylazine, and ketamine (5.0, 2.5, and 2.5 mg/kg respectfully) prior to anesthesia with morphine (0.5 mg/kg) and intravenous α-chloralose (60 mg/kg).

Experimental preparation

Anesthetized swine were intubated and ventilated with O_2-supplemented room air. Bilateral femoral cut downs were performed, and catheters placed in the femoral artery and vein. The right femoral artery catheter provided continuous measurement of systemic blood pressure and heart rate, while the venous catheter allowed for administration of anesthetic, dobutamine, and Hespan (6% hetastarch in 0.9% sodium chloride). The left 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 [8]. Arterial blood gases were analyzed periodically and adjustments to respiration were made to maintain parameters within physiological limits.

Succinylcholine (0.5 mg/kg) was administered prior to a thoracotomy in the left fifth intercostal space. 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 Transonic

Systems flow transducer (Ithaca, New York, USA). The anterior interventricular vein was cannulated to allow for sampling of venous blood from the LAD perfusion territory. Following a ~ 15 min stabilization period, data were continuously recorded on IOX data acquisition software (EMKA Technologies; Falls Church, VA).

Experimental protocol

Pigs were randomly assigned to one of the following groups: (1) control ($n = 7$); (2) hemodilution ($n = 6$); (3) hemodilution + dobutamine ($n = 5$). Hemodilution was performed by gradually replacing equal volumes of blood with the synthetic plasma expander, Hespan (6% hetastarch in 0.9% sodium chloride) at 37 °C until hematocrit was reduced ~ 50% from baseline [28]. Dobutamine was administered by an intravenous drip (250 mg/L in saline) that was titrated to increase heart rate ~ 75–100% above baseline levels.

Following a subsequent stabilization period of ~ 15 min, pressure–flow autoregulation was assessed by reducing coronary perfusion pressure (CPP) in increments of 10 mmHg from 140 to 40 mmHg. Arterial and coronary venous blood samples were simultaneously collected once hemodynamic parameters stabilized at each CPP. Coronary Pzf was assessed at 20 mmHg increments by clamping the perfusion circuit and allowing coronary blood flow to cease for ~ 4 s. Following completion of experimental protocols, hearts were fibrillated and excised as recommended by the American Veterinary Medical Association Guide on Euthanasia.

As previously reported by our laboratory and others [3, 8, 26], closed-loop autoregulatory gain (Gc) was calculated from the following formula:

$$\mathrm{Gc} = 1 - \frac{\Delta F/F}{\Delta P/P},$$

where ΔF is the change in coronary blood flow, and F is the coronary flow measured at given perfusion pressure (P). Gc was determined in 20 mmHg increments over CPPs ranging from 120 to 60 mmHg. A Gc value of 1 reflects perfect autoregulation and values < 0 indicate no autoregulation. 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, glucose, lactate, and oxygen content with an Instrumentation Laboratories automatic blood gas analyzer (GEM Premier 3000) and CO-oximeter (682) system. LAD perfusion territory was estimated to be 30% of total heart weight, as previously described [23]. MVO_2 was calculated by multiplying coronary blood flow by the coronary arterial–venous difference in oxygen content.

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: treatment

group). Differences were considered statistically significant when $P < 0.05$. If significance with ANOVA was detected, a Student–Newman–Keuls multiple comparison test 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. Statistical analyses were performed with Sigma Plot 11.0 software (Systat Software Inc., San Jose, CA, USA). Multiple linear regression analysis was performed with VassarStats (Arlington, New York, 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. Blood gas values for control swine at CPP = 100 mmHg averaged: arterial pH (7.55 ± 0.02), PCO_2 (39 ± 2 mmHg), and PO_2 (177 ± 7 mmHg), and were not significantly altered by CPP, hemodilution, or the administration of dobutamine. Reducing hematocrit from ~ 33% (control) to ~ 17% (hemodilution) markedly increased coronary blood flow ($P < 0.001$), but did not significantly affect blood pressure ($P = 0.07$), heart rate ($P = 0.21$), or MVO_2 ($P = 0.44$). Administration of dobutamine following hemodilution resulted in substantial increases in heart rate, MVO_2, and coronary blood flow despite reductions in mean aortic pressure at CPP ≤ 100 mmHg ($P < 0.001$).

Effects of hemodilution ± dobutamine-induced increases in MVO_2 on coronary blood flow and resistance as CPP was reduced from 140 to 40 mmHg are shown in Fig. 1. In untreated control swine, coronary resistance decreased linearly as CPP was reduced from 120 to 60 mmHg (Fig. 1b). Over this range of CPPs, the slope of the relationship between coronary blood flow and CPP equaled 0.0038 mL/min/g/mmHg (Fig. 1a) and autoregulatory gain averaged 0.36 ± 0.07. Significant reductions in coronary resistance (~ 50% relative to control) produced by hemodilution resulted in a modest increase in the slope of the coronary flow vs. CPP relationship (0.0085 mL/min/g/mmHg; $P = 0.03$), but did not significantly affect autoregulatory gain (0.33 ± 0.1; $P = 0.78$). Hemodilution + dobutamine caused further reductions in coronary resistance (> 75% relative to control), a marked increase in the slope of the relationship between coronary blood flow and CPP (0.025 mL/min/g/mmHg; $P < 0.001$), and a significant reduction in autoregulatory gain (− 0.01 ± 0.03; $P < 0.01$).

Effects of coronary venous PO_2 on coronary pressure–flow autoregulation

Coronary venous PO_2 decreased as CPP was lowered from 140 to 40 mmHg in each of the treatment groups (Table 1). Although group differences in coronary venous PO_2 were detected by ANOVA between hemodilution + dobutamine vs. control swine ($P < 0.01$), average values remained < 29.0 ± 2.6 mmHg in all groups and no differences were found by multiple comparison test at any given CPP. Regression analysis of all data revealed that differences in coronary resistance produced by hemodilution ± dobutamine were not predicted by underlying differences in myocardial oxygen tension, as coronary venous PO_2 changed over very similar ranges in all groups (Fig. 2a). To assess the relationship between coronary venous PO_2 and autoregulatory capacity, changes in coronary blood flow (20

mmHg increments from 140 to 40 mmHg) and 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 neither changes in coronary blood flow (Fig. 2b; $P = 0.29$) nor autoregulatory gain (Fig. 2c; $P = 0.12$) were significantly related to coronary venous PO_2.

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 Fig. 3. Occlusion of the coronary perfusion circuit resulted in a rapid reduction in coronary blood flow and stabilization of coronary pressure at zero flow within ~ 3–4 s of the occlusion. Consistent with previous studies in the literature [14, 15, 17, 30, 41, 47], coronary Pzf was directly related with underlying coronary vascular tone as Pzf decreased from 25.0 ± 0.7 mmHg at CPP = 100 mmHg in control swine, to 21.2 ± 1.8 mmHg following hemodilution ($P < 0.05$), and to 14.8 ± 1.4 mmHg in the hemodilution + dobutamine group ($P < 0.001$) (Table 1). Coronary Pzf also decreased ~ 40% as CPP was lowered from 140 to 40 mmHg in each of the treatment groups ($P < 0.001$). Thus, Pzf was closely related to overall coronary vascular resistance ($r = 0.71$; $P < 0.001$) (Fig. 4). Examination of the relationship between coronary vascular tone (indexed by Pzf) and the change in coronary blood flow (20 mmHg increments from 140 to 40 mmHg) revealed relatively minimal changes in flow at Pzf > 20 mmHg and that the greatest changes in coronary flow occurred below this threshold value ($r = 0.68$; $P < 0.001$) (Fig. 4b). Coronary Pzf was also positively correlated with autoregulatory gain ($r = 0.43$; $P = 0.001$) (Fig. 4c).

Discussion

The question surrounding the mechanism(s) responsible for coronary pressure–flow autoregulation has been central to the field of coronary physiology since the 1950s [1, 7, 39]. The contention that myocardial oxygen tension determines the degree of autoregulatory behavior and thus that the primary mechanism of autoregulation is metabolic in nature has dominated since the seminal study of Dole and Nuno in 1986 [16]. However, we submit that there are reasons to challenge this hypothesis, in that coronary vasodilation not only augments coronary venous PO_2, “uncoupling” the balance between flow and metabolism, but functionally antagonizes the intrinsic smooth muscle (myogenic) response to changes in pressure [34, 37]. We propose the necessary experiment to more directly examine this fundamental issue to establish conditions in which underlying coronary tone (resistance) is altered, without appreciable changes in coronary venous PO_2. To achieve these states, we performed autoregulatory experiments (CPPs ranging from 140 to 40 mmHg) in the absence and presence of euvolemic hemodilution (~ 50% reduction in hematocrit), with and without the administration of dobutamine to augment MVO_2. Findings from the present studies support that coronary autoregulatory behavior is predominantly dependent on an adequate degree of underlying vasomotor tone, independent of normal myocardial oxygen tension (coronary venous PO_2).

Metabolic control and coronary autoregulatory capacity

The fundamental observation in support of the metabolic hypothesis of coronary autoregulation is the consistent result in this (Table 1) and prior studies [8, 26, 42, 45, 48] that coronary venous PO_2 declines with reductions in CPP. This finding along with the inverse relationship between autoregulatory gain and coronary venous PO_2 [3, 16] implicates the active production of dilator metabolites in proportion to pressure-dependent reductions in tissue oxygenation. However, an alternative interpretation of these findings is that the loss of autoregulation in vasodilated preparations is a consequence of the lack of an adequate vasomotor tone (or reserve) that results in “over-perfusion” and an increase in coronary venous PO_2, as opposed to support of a causal role for metabolic control per se. Data from the present study offer a unique examination of these contrasting interpretations, as values of coronary venous PO_2 remained quite similar between groups over the wide CPP range of 140–40 mmHg and stayed (on average) below the 32 mmHg autoregulatory threshold previously established by Dole and Nuno [16]. It is important to recognize that prior studies have consistently shown that the level of the steady state pressure–flow relationship directly adjusts to the level of MVO_2; however, they have also definitively demonstrated that the strength of the autoregulatory response is independent of MVO_2 [16, 18, 21, 38, 46]. As such, the complete loss of autoregulation in the hemodilution + dobutamine group (Fig. 1a) is neither predicted nor explained by the metabolic hypothesis. Further examination of the relationship between myocardial oxygen tension and the degree of autoregulation revealed that the level of coronary venous PO_2 was not predictive of changes in coronary blood flow (Fig. 2b) or autoregulatory gain (Fig. 2c). Taken together, these findings directly refute that normal myocardial oxygen tension is requisite for coronary pressure–flow autoregulation. It should be recognized that this conclusion relies on the assumption that coronary venous PO_2 provides a realistic estimate of myocardial tissue PO_2 [22], which remains to be definitively established.

Coronary vasomotor tone, Pzf, and autoregulatory capability

To examine the effect of coronary vasomotor tone on autoregulatory capacity, we elected to measure coronary Pzf at 20 mmHg increments across all treatment groups. Our rationale was based on numerous earlier studies which established that Pzf was predominantly determined by underlying vascular smooth muscle tone [14, 15, 17, 30, 41, 47]. Pzf was determined in the present study by stopping/clamping the extracorporeal coronary perfusion circuit for ~ 4 s while the heart continued to beat (Fig. 3). As such, determination of Pzf in this manner relates to the decay of pressure as a function of resistance and capacitance of the system. It should be noted that prior measurements of coronary Pzf utilized a variety of different means, typically vagal stimulation (long diastole) but also by decreasing aortic or extracorporeal reservoir pressure, AV node ablation and pacing, and/or occlusion of perfusion circuit in both beating and non-beating hearts [2, 5, 14, 15, 20, 27, 29, 32, 43]. Although the values of coronary Pzf may differ between these conditions, 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 significantly reduced by hemodilution and hemodilution + dobutamine at a given CPP as well as diminished by reductions in CPP across all treatment groups. Therefore, while interpretation of coronary Pzf has been controversial [30, 41], there is strong evidence that measurements of Pzf serve

as an objective and reliable index of underlying coronary vascular tone, as coronary Pzf was directly related to coronary vascular resistance across all treatment groups in this study (Fig. 4a). Use of an alternative estimate of coronary resistance (CPP minus Pzf divided by coronary blood flow) does not affect any of the relationships or conclusions of the study.

Analysis of individual data points from all treatment conditions demonstrates that coronary Pzf (vasomotor tone) is highly predictive of changes in coronary blood flow (Fig. 4b) and autoregulatory gain (Fig. 4c). More careful examination of these relationships reveals that the changes in blood flow were the greatest, and autoregulatory gain the lowest, when values of coronary Pzf fell below ~ 20 mmHg. These findings illustrate that coronary pressure–flow autoregulation is dependent on an adequate degree of underlying vasomotor tone and thus consistent with an intrinsic, pressure-dependent mechanism within the vasculature that is progressively impaired by reductions in overall resistance. Attenuation of the myogenic response with diminished coronary tone is evident in previous studies, which have compared changes in coronary diameter in isolated, pressurized arterioles with varying degrees of underlying vasomotor tone [34, 37]. To illustrate this point, we calculated a myogenic index (MI) on data from swine and human arterioles, in which the slope of the active pressure–diameter relationship at a given pressure was determined using the following equation:

$$\mathrm{MI} = 100 \times \frac{\left(D_f - D_i\right)/D_i}{P_f - P_i}$$

where D_i and D_f are the initial and final diameters, while P_i and P_f are the initial and final intraluminal pressures. The more negative the myogenic index, the greater is the myogenic responsiveness [12]. Determination of the MI using data from Kuo et al. [34] and Miller et al. [37] demonstrates that vessels with less tone are less myogenically responsive (Fig. 5). The present findings are consistent with this paradigm, in that autoregulation is evident in the presence of hemodilution, i.e., when there was a sufficient level of tone (myogenic reserve), and absent following the administration of dobutamine, when there was an insufficient level of vasomotor reserve. It is important to recognize that values of coronary blood flow in the hemodilution + dobutamine group (highest average = 3.44 ± 0.42 mL/min/g) were far from established maximal levels of coronary flow which reach ~ 5.0 mL/min/g [44]. Thus, the loss of autoregulation in this group does not reflect the complete loss of tone or vasodilator reserve; i.e., a passive coronary vasculature.

Implications and conclusions

Findings from this investigation demonstrate that the local metabolic hypothesis as classically proposed is not sufficient to explain coronary autoregulatory behavior and suggest that the primary mechanism of coronary autoregulation is likely more myogenic in origin. This conclusion is consistent with prior studies which documented that $Ca_V1.2$ channels are critical for the coronary myogenic response [37] and that inhibition of these channels abolishes coronary autoregulation in vivo [8]. Furthermore, previous mathematical modeling studies also support that myogenic behavior is required for and independently necessary to explain pressure–flow autoregulation in the coronary circulation [9, 10, 13]. While our findings do not support myocardial tissue oxygen tension as an essential feedback

signal for the autoregulatory response, they do not completely rule out a role for "metabolites" either. However, we submit that our understanding of metabolic control of coronary blood flow is sorely lacking and it is clear that prior studies which inhibited pathways implicated in maintaining myocardial oxygen supply/demand balance in response to exercise (H_2O_2/K_V channels [8]; purine nucleotides/$P2Y_1$ receptors [6]), anemia (K_{ATP} channels [19, 42]), or ischemia (adenosine [17, 19, 25, 31]; nitric oxide [40]) have all failed to show significant alterations in the coronary autoregulatory response. Nonetheless, the current results directly challenge that normal myocardial oxygen tension is required for coronary pressure–flow autoregulation and thus argue against a requisite role for local metabolic control of coronary resistance in response to changes in perfusion pressure.

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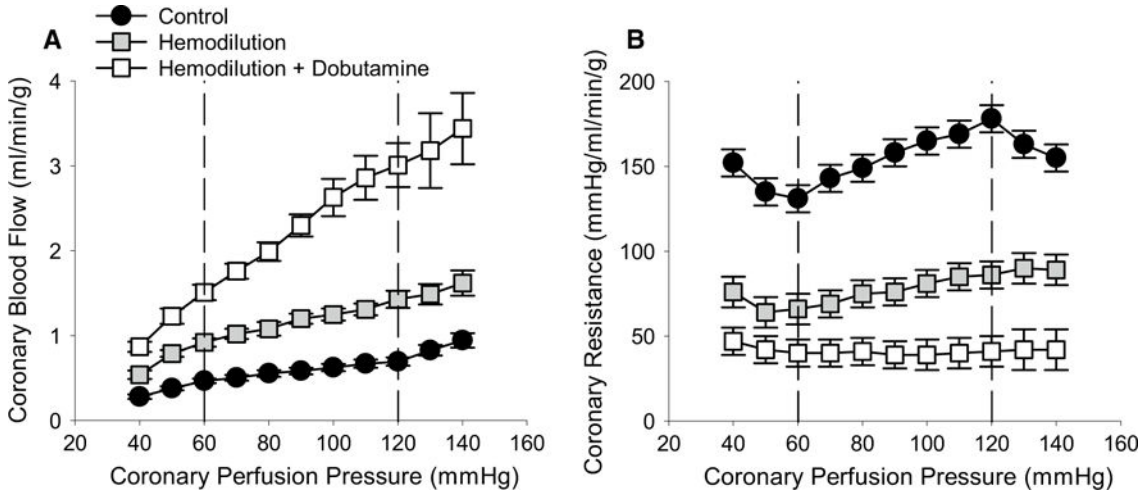

Fig. 1.

Effects of alterations in coronary tone and myocardial oxygen consumption on coronary pressure–flow autoregulation. **a** Coronary blood flow increased at a given CPP as vasomotor tone was decreased: control ($n = 7$) > hemodilution ($n = 6$) > hemodilution + dobutamine ($n = 5$). Relative to untreated control swine, the slope of flow–pressure relationship within the autoregulatory range (CPP 120–60 mmHg) was significantly increased by hemodilution ($P = 0.03$) and hemodilution + dobutamine ($P < 0.001$). **b** Average coronary vascular resistance was significantly reduced by hemodilution ($P < 0.001$) and hemodilution + dobutamine ($P < 0.001$)

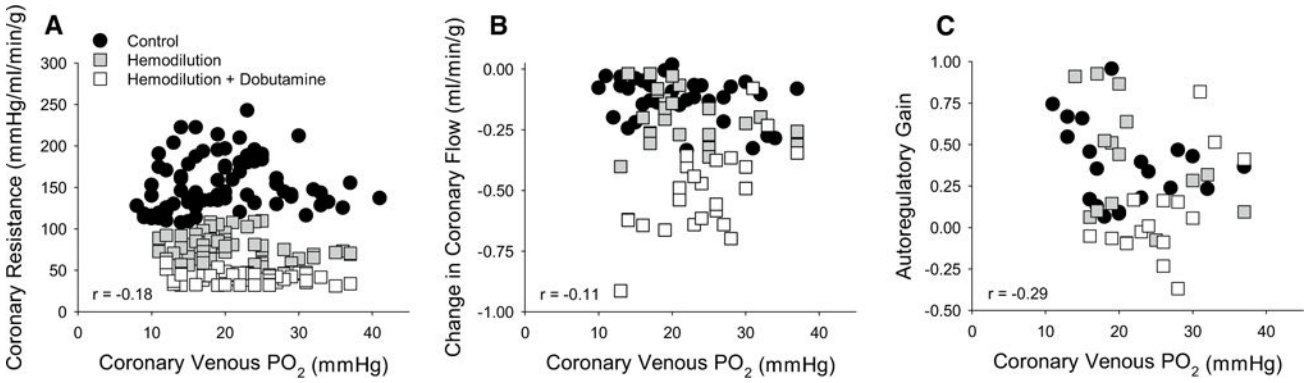

Fig. 2.

Relationship between coronary venous PO_2 and coronary autoregulatory capacity. **a** Coronary venous PO_2 decreased over similar ranges as CPP was lowered from 140 to 40 mmHg in all groups: control ($n = 7$); hemodilution ($n = 6$); hemodilution + dobutamine ($n = 5$). However, coronary venous PO_2 was not predictive of coronary resistance. **b** Coronary venous PO_2 was not associated with changes in coronary blood flow (20 mmHg increments) or **c** overall autoregulatory gain (CPP ranging from 120 to 60 mmHg) across treatment groups

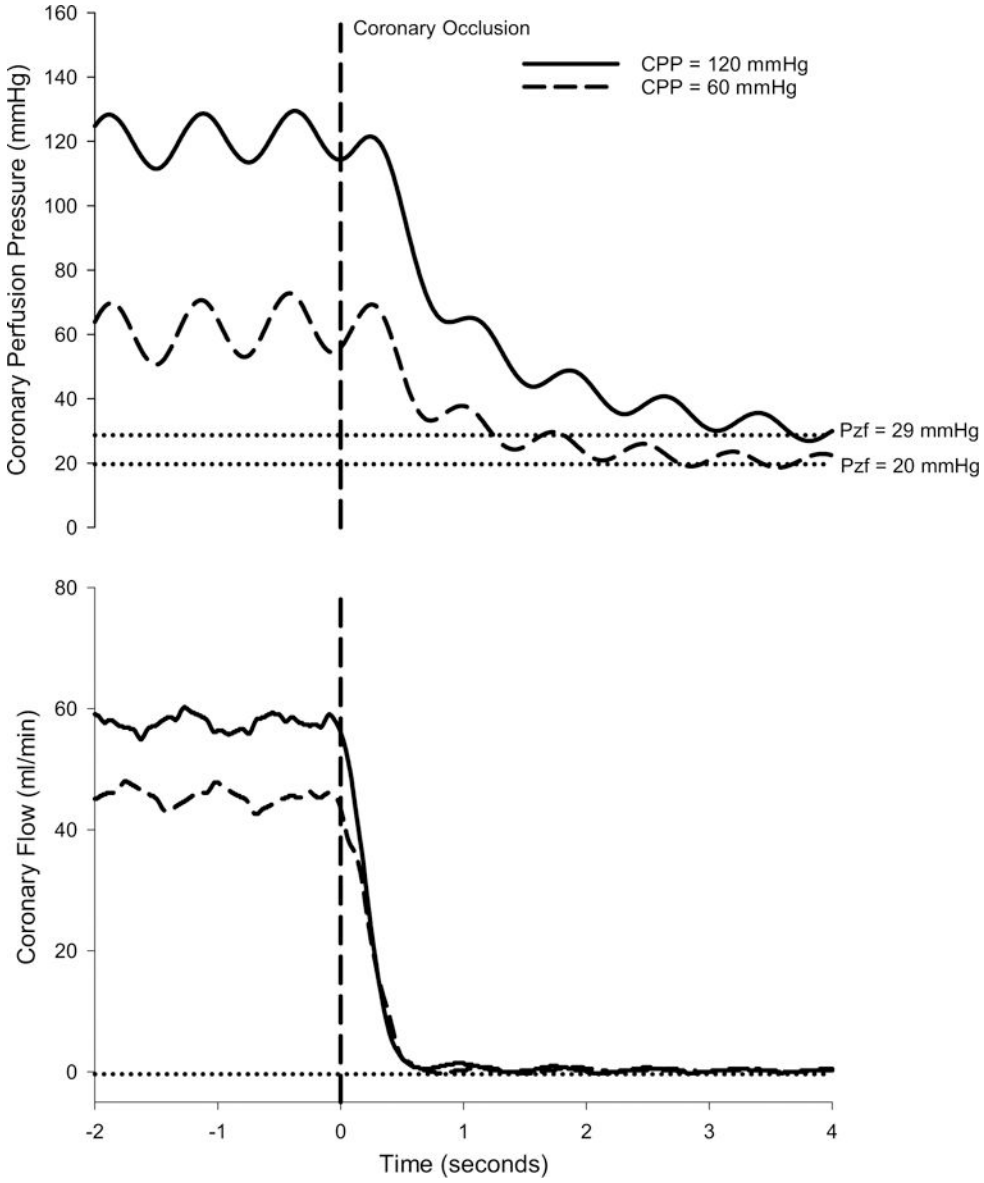

Fig. 3.

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)

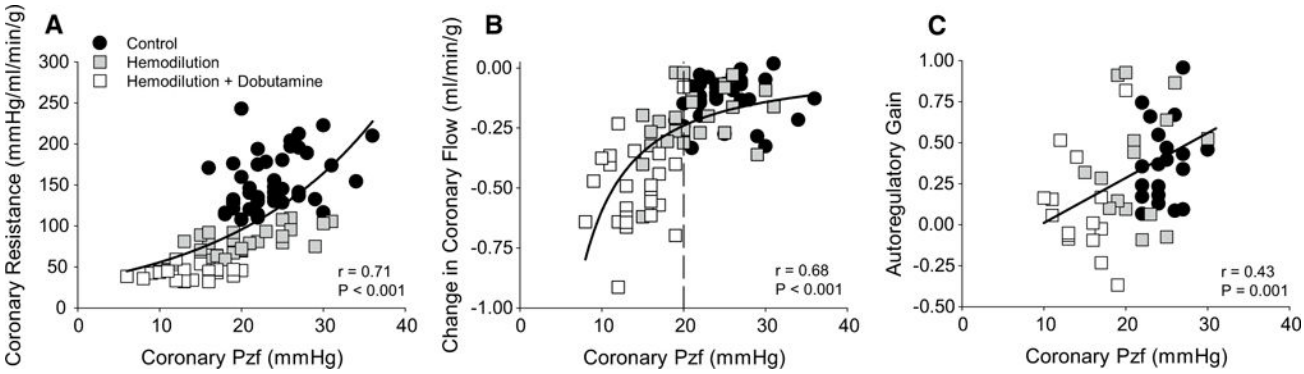

Fig. 4.

Relationship between coronary zero-flow pressure (Pzf) and coronary autoregulatory capacity. **a** 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 ($n = 5$). **b** Changes in coronary blood flow (20 mmHg increments) remained modest at Pzf > 20 mmHg and significantly decreased below this threshold value. **c** Autoregulatory gain (CPP ranging from 120 to 60 mmHg) was positively correlated with coronary Pzf

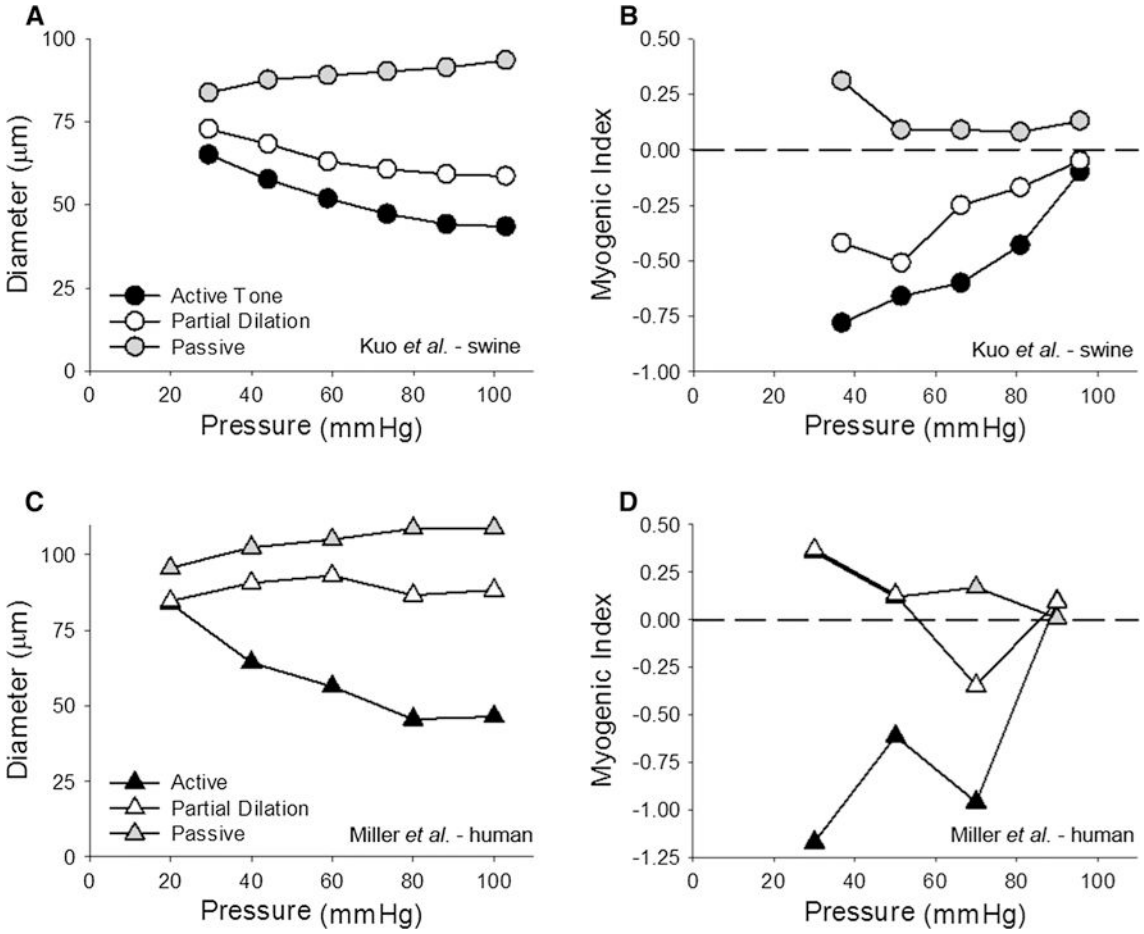

Fig. 5.

Myogenic reactivity is decreased by vasodilator influences. Data are from Kuo et al. [34] in **a** and **b** and from Miller et al. [37] in **c** and **d**. **a**, **c** The pressure–diameter relationship for coronary arterioles under three different conditions of tone: (a) in the active state (control); (b) when partially dilated; (c) passive (no tone). **b**, **d** Contain the respective analysis of myogenic index. The more negative the numbers, the more myogenically active an arteriole is. Positive values indicate pressure-induced dilation

Table 1

Hemodynamic and coronary responses to graded changes in perfusion pressure

Coronary per-fusion pressure (mmHg)	140	130	120	110	100	90	80	70	60	50	40	CPP	Group	Interaction
Mean aortic pressure (mmHg)														
Control	87 ± 7	87 ± 6	88 ± 6	88 ± 6	88 ± 6	87 ± 6	88 ± 6	88 ± 6	87 ± 6	87 ± 6	85 ± 6	$P = 0.34$	$P < 0.001$	$P = 0.79$
Hemodilution	86 ± 8	86 ± 8	81 ± 8	81 ± 7	80 ± 8	80 ± 8	80 ± 8	80 ± 8	84 ± 8	83 ± 8	82 ± 8			
Hemodilution + dobutamine	91 ± 9	84 ± 8	74 ± 7	73 ± 6	66 ± 7†	62 ± 6†	60 ± 5†	59 ± 4†	59 ± 5†	58 ± 5†	58 ± 5†			
Heart rate (beats/min)														
Control	74 ± 4	77 ± 3	75 ± 4	75 ± 4	77 ± 4	76 ± 4	77 ± 4	78 ± 4	78 ± 4	79 ± 4	80 ± 4	$P = 0.72$	$P < 0.001$	$P = 0.99$
Hemodilution	75 ± 6	75 ± 6	72 ± 6	71 ± 5	72 ± 5	73 ± 5	73 ± 4	73 ± 4	77 ± 3	77 ± 3	78 ± 3			
Hemodilution + dobutamine	152 ± 8†	151 ± 8†	134 ± 11†	134 ± 9†	142 ± 7†	140 ± 6†	139 ± 5†	140 ± 5†	142 ± 5†	143 ± 5†	140 ± 4†			
Hematocrit (%)														
Control	32 ± 2	32 ± 2	32 ± 2	32 ± 2	33 ± 2	33 ± 2	33 ± 2	33 ± 2	33 ± 2	34 ± 2	33 ± 2	$P = 1.00$	$P < 0.001$	$P = 1.00$
Hemodilution	17 ± 2†	16 ± 2†	16 ± 2†	16 ± 2†	16 ± 2†	17 ± 2†	17 ± 3†	16 ± 2†	16 ± 2†	17 ± 2†	16 ± 3†			
Hemodilution + dobutamine	18 ± 5†	18 ± 6†	21 ± 4†	21 ± 4†	21 ± 4†	21 ± 4†	20 ± 4†	20 ± 4†	19 ± 3†	19 ± 4†	19 ± 3†			
Coronary blood flow (mL/min/g)														
Control	0.95 ± 0.09*	0.83 ± 0.06*	0.70 ± 0.05	0.67 ± 0.05	0.63 ± 0.04	0.58 ± 0.04	0.56 ± 0.04	0.50 ± 0.03	0.47 ± 0.03	0.38 ± 0.02*	0.28 ± 0.03*	$P < 0.001$	$P < 0.001$	$P < 0.001$
Hemodilution	1.62 ± 0.15*†	1.49 ± 0.12†	1.43 ± 0.1†	1.31 ± 0.07†	1.25 ± 0.07†	1.20 ± 0.06†	1.08 ±s 0.08†	1.02 ± 0.06†	0.92 ± 0.05*†	0.79 ± 0.04*†	0.54 ± 0.05*†			
Hemodilution + dobutamine	3.44 ± 0.42†	3.18 ± 0.44†	3.01 ± 0.26†	2.86 ± 0.26†	2.63 ± 0.22†	2.30 ± 0.13†	1.99 ± 0.11*†	1.76 ± 0.09*†	1.51 ± 0.09*†	1.23 ± 0.09*†	0.87 ± 0.06*†			
MVO_2 (μL O_2/min/g)														
Control	63 ± 2	61 ± 5	57 ± 6	62 ± 5	62 ± 6	62 ± 6	61 ± 5	58 ± 5	56 ± 4	49 ± 4	37 ± 5*	$P < 0.001$	$P < 0.001$	$P = 0.16$
Hemodilution	70 ± 12	69 ± 9	59 ± 8	58 ± 8	56 ± 4	53 ± 3	54 ± 3	51 ± 2	44 ± 4	40 ± 4	30 ± 2			
Hemodilution + dobutamine	175 ± 28†	159 ± 36†	128 ± 29†	130 ± 30†	130 ± 24†	104 ± 26†	101 ± 24†	98 ± 22†	81 ± 14	73 ± 11	60 ± 9			
Coronary venous PO_2 (mmHg)														
Control	28.7 ± 1.9	27.7 ± 3.0	25.0 ± 3.0	22.6 ± 2.5	20.1 ± 1.9	18.9 ± 2.4	17.6 ± 2.1	16.0 ± 2.0	15.4 ± 1.7	14.0 ± 1.9	13.4 ± 2.2	$P < 0.001$	$P < 0.001$	$P = 0.97$
Hemodilution	24.8 ± 3.4	25.0 ± 3.3	28.7 ± 5.3	26.8 ± 4.5	21.2 ± 2.9	24.8 ± 4.5	19.8 ± 2.7	19.2 ± 2.7	17.2 ± 2.1	16.2 ± 2.5	15.6 ± 2.3			
Hemodilution + dobutamine	26.0 ± 2.3	26.0 ± 1.7	29.0 ± 2.6	28.2 ± 2.4	26.4 ± 2.8	26.3 ± 2.0	24.7 ± 2.3	22.5 ± 2.2	20.3 ± 2.3	18.8 ± 2.2	16.8 ± 1.4			
Pzf (mmHg)														
Control	30.3 ± 1.6*		27.0 ± 1.0		25.0 ± 0.7		22.9 ± 0.5		20.6 ± 0.4*		18.4 ± 0.5*	$P < 0.001$	$P < 0.001$	$P = 0.38$s

Coronary per-fusion pressure (mmHg)	140	130	120	110	100	90	80	70	60	50	40	CPP	Group	Interaction
Hemodilution	26.2 ± 1.9 *†		24.2 ± 1.8		21.2 ± 1.8 †		18.8 ± 0.7 †		16.2 ± 0.7 *†		15.2 ± 0.7 *†			
Hemodilution + dobutamine	16.0 ± 1.7 †		15.6 ± 1.5 †		14.8 ± 1.4 †		13.5 ± 1.1 †		11.7 ± 1.2 †		10.5 ± 1.2 †			

* $P < 0.05$ vs CPP 100 mmHg within the group

† $P < 0.05$ vs control at the same CPP