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Open-loop (feed-forward) and feedback control of coronary blood flow during exercise, cardiac pacing, and pressure changes

Ranjan K. Pradhan,1 Eric O. Feigl,2 Mark W. Gorman,2 George L. Brengelmann,2 and Daniel A. Beard1

1Department of Molecular and Integrative Physiology, University of Michigan, Ann Arbor, Michigan; and 2Department of Physiology and Biophysics, University of Washington, Seattle, Washington

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Pradhan RK, Feigl EO, Gorman MW, Brengelmann GL, Beard DA. Open-loop (feed-forward) and feedback control of coronary blood flow during exercise, cardiac pacing, and pressure changes. Am J Physiol Heart Circ Physiol 310: H1683–H1694, 2016. First published April 1, 2016; doi:10.1152/ajpheart.00663.2015.—A control system model was developed to analyze data on in vivo coronary blood flow regulation and to probe how different mechanisms work together to control coronary flow from rest to exercise, and under a variety of experimental conditions, including cardiac pacing and with changes in coronary arterial pressure (autoregulation). In the model coronary flow is determined by the combined action of a feedback pathway signal that is determined by the level of plasma ATP in coronary venous blood, an adrenergic open-loop (feed-forward) signal that increases with exercise, and a contribution of pressure-mediated myogenic control. The model was identified based on data from exercise experiments where myocardial oxygen extraction, coronary flow, cardiac interstitial norepinephrine concentration, and arterial and coronary venous plasma ATP concentrations were measured during control and during adrenergic and purinergic receptor blockade conditions. The identified model was used to quantify the relative contributions of open-loop and feedback pathways and to illustrate the degree of redundancy in the control of coronary flow. The results indicate that the adrenergic open-loop control component is responsible for most of the increase in coronary blood flow that occurs during high levels of exercise. However, the adenine nucleotide-mediated metabolic feedback control component is essential. The model was evaluated by predicting coronary flow in cardiac pacing and autoregulation experiments with reasonable fits to the data. The analysis shows that a model in which coronary venous plasma adenine nucleotides are a signal in local metabolic feedback control of coronary flow is consistent with the available data.

NEW & NOTEWORTHY

Coronary blood flow varies to match oxygen delivery to myocardial oxygen demand. Integrating sympathetically mediated open-loop and metabolic adenine nucleotide-mediated feedback control in a model of coronary blood flow control shows how these pathways work together and illustrates the central role of feedback in the control of coronary blood flow.

OVER AN APPROXIMATELY fourfold range of rate of oxygen consumption, the myocardium extracts ~80% of the oxygen from the blood passing through the coronary circulation. Therefore, coronary blood flow and the rate of oxygen consumption are closely matched in vivo. Coronary blood flow is controlled through several partially redundant mechanisms (17, 19). These mechanisms include open-loop control (in which signals that elicit an increase in cardiac oxygen consumption have a parallel effect of eliciting an increase in blood flow), feedback control (in which a variable that increases with an increasing degree of oxygen supply/consumption mismatch elicits increases in flow), and myogenic control (in which a change in transmural pressure elicits a change in active tension in the vascular wall). Open-loop (or feed-forward) control is mediated primarily through vasodilation by stimulation of $\beta_1$ and $\beta_2$-adrenoceptors, and vasoconstriction by stimulation of $\alpha$-adrenoceptors on coronary vascular smooth muscle cells (4, 13, 24, 27). Sympathetic activation also induces physiological increases in myocardial oxygen consumption via activation of myocardial $\beta$-adrenoceptors (12, 13, 27). The feedback pathway is postulated to take the form of a local oxygenation-dependent signal that elicits vasodilation in response to decreased oxygen supply and/or increased oxygen metabolism. The plasma concentration of adenine nucleotides in coronary venous blood, which are derived from red blood cells in response to desaturation of oxyhemoglobin, is postulated to be the primary feedback signal (15, 22) where ATP and its metabolites ADP and AMP activate purinergic receptors on coronary vascular endothelial cells to initiate a conducted signal that leads to upstream coronary vasodilation (21, 22) (see Fig. 1). The model analysis is based on the characterization of steady-state responses of different flow control pathways (open-loop and feedback) that captures the observed relationships between myocardial oxygen metabolism and coronary flow, under physiological conditions and pharmacological blockade of the control pathways.

The purposes of the present study are 1) to analyze experimental data on coronary blood flow and myocardial oxygen consumption in exercise and see if a simple control model can fit the available in vivo data (2, 15, 22–24); 2) to use the developed model for quantifying the relative contributions of open-loop and feedback flow control pathways with exercise; and 3) to determine if the adenine nucleotide hypothesis (15) for metabolic feedback control of coronary flow is consistent.

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with data from exercise, cardiac pacing, and autoregulation experiments (1, 39).

Glossary

**Model Variables and Fixed Parameters**

- \( N \): Interstitial fluid norepinephrine (NE) concentration, nM
- \( S_A \): Arterial oxyhemoglobin saturation, unitless
- \( S_V \): Coronary venous oxyhemoglobin saturation, unitless
- \( F \): Coronary flow, \( \text{ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1} \)
- \( g_{ol} \): Conductance of open-loop flow control pathway, \( \text{ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1} \cdot \text{mmHg}^{-1} \)
- \( g_{fb} \): Conductance of feedback flow control pathway, \( \text{ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1} \cdot \text{mmHg}^{-1} \)
- \( g_P \): Conductance of myogenic flow control pathway, \( \text{ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1} \cdot \text{mmHg}^{-1} \)
- \( G \): Total conductance, \( \text{ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1} \cdot \text{mmHg}^{-1} \)
- \( M \): Myocardial oxygen consumption rate, \( \mu \text{l} \cdot \text{O}_2 \cdot \text{min}^{-1} \cdot \text{g}^{-1} \)
- \( P \): Mean arterial pressure, mmHg
- \( C_o \): Oxygen content of blood when oxyhemoglobin is fully saturated and hematocrit is 100%, neglecting dissolved oxygen, \( \mu \text{l} \cdot \text{O}_2 / \text{ml} \)
- \( H \): Hematocrit, %
- \( V_c \): Capillary volume density, ml/g
- \( T_V \): Concentration of coronary venous plasma ATP, nM

**Adjustable Model Parameters**

- \( K_M \): A constant relating myocardial oxygen metabolism to interstitial norepinephrine concentration, \( \mu \text{l} \cdot \text{O}_2 \cdot \text{min}^{-1} \cdot \text{g}^{-1} \cdot \text{nM}^{-1} \)
- \( M_o \): Myocardial oxygen consumption rate (when ISF[NE] = 0), \( \mu \text{l} \cdot \text{O}_2 \cdot \text{min}^{-1} \cdot \text{g}^{-1} \)
- \( J_0 \): ATP release rate in coronary vascular bed, \( \mu \text{M} / \text{min} \)
- \( S_0 \): ATP release parameter of the model, unitless
- \( T_A \): Concentration of arterial plasma ATP, nM

**Materials and Methods**

Experimental Data for Coronary Blood Flow Control Model

Hemodynamic data used to characterize different flow control pathways were obtained from four previously published studies from the Feigl laboratory (15, 22–24). All control studies were done using conscious dogs under both resting conditions and treadmill exercise. Experiments with pharmacological interventions were conducted under similar exercise conditions in which \( \alpha \)-adrenoceptors were blocked by phentolamine administration (23, 24), and \( \alpha \) - and \( \beta \)-adrenoceptors were blocked by both phentolamine and propranolol administration (23, 24). Purinergic vasodilation was inhibited by blocking endothelial purinergic receptors (P1 and P2Y1) with 8-phenyltheophylline (8-PT) and MRS 2500, and L-nitroarginine (LNA) to block conducted vasodilator signaling from the capillary to the upstream arteriole (22).

The total data set used here for model identification includes measurements of coronary flow, myocardial oxygen consumption, coronary arterial and venous oxyhemoglobin saturations, hematocrit levels, and mean arterial pressure from 26 animals under various treatments and exercise levels. There were 20 scattered missing values of the 1,228 primary measurements. The average value of the relevant treatment and exercise subgroup was used to replace the missing values. Data from one dog were excluded from the published data because of an artifact. In this case measured coronary venous oxyhemoglobin saturation was normal (12.3%) immediately after placement of the coronary sinus catheter, but was 34.5% ten days later on the day of the experiment, indicating that it had slipped part way out and was sampling a mixture of coronary venous and right atrial blood. This was not recognized at the time the data were assembled for publication. One [ATP] measurement was 9.5 standard deviations above the...
The overall architecture of the model is shown in Fig. 2. It has four main components.

1) Open-loop control. Open-loop control, also called “feed-forward” or “yoked (parallel)” control, where myocardial oxygen metabolism and adrenergic blood flow control are simultaneously modulated by sympathetic discharge to the myocardium and the coronary vessels (5, 17, 19, 23), is one component. This open-loop control is incorporated into blocks 4 and 5 of the model, as detailed below.

2) Feedback control. Feedback control, where the rate ATP release from red blood cells increases with decreasing oxyhemoglobin saturation acts on vascular endothelial purinergic receptors to stimulate a conducted response to increased myocardial oxygen metabolism. The model shown in Fig. 2 includes feedback pathways by purinergic receptor blocking agents. A block diagram representation of the model showing various pathway functions, which includes no time-dependency and thus applies only to physiological steady states, is shown in Fig. 2.

Block 1: ATP Release and Transport

It is assumed that oxygen saturation in a capillary decreases linearly from the arterial to venous end:

\[ S(l) = S_A + I(S_V - S_A), \quad 0 \leq I \leq 1 \]  

where \( I \in (0, 1) \) represents the position along the capillary with \( I = 0 \) at the arterial end and \( I = 1 \) at the venous end. The variables \( S_A \) and \( S_V \) represent the arterial \( S = S_A \) and venous \( S = S_V \) oxyhemoglobin saturation.

Plasma ATP transport is governed by release from red blood cells and advection in the blood. Assuming that the rate of ATP release...
from red blood cells declines exponentially with red blood cell oxygen saturation, the steady-state continuity equation for plasma ATP concentration \(T\) is

\[
\frac{\partial T}{\partial t} = -\frac{V_e}{F}J_T - \frac{V_e}{F}J_0 e^{\frac{T - T_0}{T_0}}
\]

where \(J_T\) is the rate of ATP release into plasma, which is assumed proportional to hematocrit, \(H\). The variable \(F\) represents the blood flow; the constant \(V_e\) is the capillary volume density in the myocardium (set to 0.04 ml/g); \(J_0\) and \(S_0\) are adjustable parameters.

Equation 2 has solution

\[
T(\hat{t}) = \frac{V_e}{F(S_A - S_0)} e^{\frac{S_A}{S_0} e^{(S_A - S_0)\hat{t}} - 1} + T_A
\]

where \(T_A\) is the arterial plasma ATP concentration, \(T_A = T(0)\), and \(\hat{t}\) is an adjustable parameter.

Block 1 in the overall coronary flow control model outputs venous plasma ATP concentration \(T_v\) based on the input flow and metabolic rate:

\[
T_v = \frac{V_e}{F(S_A - S_0)} e^{\frac{S_A}{S_0} e^{(S_A - S_0)\hat{t}} - 1} + T_A
\]

The model for block 1 involves three adjustable parameters \(J_0, S_0,\) and \(T_A\) to match observations (15) on coronary venous plasma [ATP] at different flows and venous oxyhemoglobin saturation. Equation 4 determines the relationship between plasma [ATP], and the other variables in the model.

Block 2: ATP-Dependent Feedback Pathways Conductance

The model assumes a simple linear dependence of the feedback-mediated contribution to overall conductivity and \(T_v\):

\[
g_{fb} = K_{fb} \cdot (T_v - T_A)
\]

where \(K_{fb}\) is an adjustable parameter, the gain of the feedback pathway, and \(T_A\) is arterial plasma [ATP].

Block 3: Oxygen Mass Balance

The relationship between coronary flow \(F\), myocardial oxygen metabolism \(M\), and venous and arterial oxygen saturation is obtained from mass conservation. Specifically, the myocardial oxygen consumption is equal to the flow multiplied by the arterial-venous oxygen content difference. In terms of oxyhemoglobin saturation,

\[
M = F \cdot C_O \cdot H \cdot (S_A - S_v)
\]

where \(H\) is the hematocrit, \(C_O\) is the oxygen-carrying capacity of red blood cells, and \(C_O \cdot H\) is the oxygen content of blood at 100% oxyhemoglobin saturation. For simplicity this equation ignores the secondary contribution of dissolved oxygen to total oxygen content in the blood. Coronary venous oxyhemoglobin saturations are calculated from Eq. 6:

\[
S_v = S_A - \frac{M}{F \cdot C_O \cdot H}
\]

Block 4: Sympathetic Open-Loop Control of Coronary Flow

The signal transmitted by the open-loop pathway is assumed to be proportional to the concentration of cardiac interstitial norepinephrine \(N\):

\[
g_{ol} = K_{ol} \cdot N
\]

where \(K_{ol}\) is an adjustable parameter that represents the open-loop gain, which determines the open-loop contribution to overall conductivity. The variable \(N\) is varied from 0 to 15 nM as the input to the model.

Block 5: Effect of Sympathetic Inputs on Myocardial Oxygen Metabolism

The sympathetic input signal \(N\) simultaneously affects the myocardial oxygen metabolism \(M\), which is expressed as:

\[
M = K_M \cdot N + M_0
\]

where \(K_M\) is an adjustable parameter that determines the relationship between \(M\) and \(N\) from resting to exercise conditions. This parameter \(K_M\) is identified from experimental estimates of myocardial \(N\) measured as a function \(M\) in conscious exercising animals. The adjustable parameter \(M_0\) is the myocardial oxygen metabolism at zero \(N\), identified from control experiments (24).

Block 6: Myogenic Control of Coronary Flow

Pressure-mediated myogenic control is modeled using simple linear relationship between arterial pressure \(P\) and myogenic contribution to conductance:

\[
g_p = -K_{myo} \times P
\]

where \(K_{myo}\) is an adjustable parameter, representing myogenic gain of the pressure-flow relationship. The parameter \(K_{myo}\) determines the contribution of arterial pressure change to net vascular conductance.

Total Conductance

The net conductance \(G\) of coronary vasculature is defined as the summation of conductance of open-loop, feedback, myogenic, and basal conductance \(g_0\),

\[
G = g_{ol} + g_{fb} + g_p + g_0
\]

The contribution to flow of the open-loop and feedback pathways can be calculated as the conductance of these pathways \((g_{ol} + g_{fb})\) times the mean arterial pressure \(P\). The coronary flow is computed from the pressure \(P\) and total conductance \(G\).

\[
F = G \cdot P
\]

At given values of the inputs \(N\) and \(P\), Eqs. 4–11 are solved as follows:

1) The variables \(g_{ol}, M,\) and \(g_p\) are computed directly from Eqs. 7, 8, and 9.

2) The five remaining unknowns \(F, S_v, T_v, g_{fb},\) and \(G\) are determined numerically by satisfying Eqs. 4, 5, 6, 10, and 11. These equations include four fixed constants \(V_e, H, S_A,\) and \(C_O\), and a total of eight adjustable parameters \(J_0, S_0, T_A, K_M, M_0, K_{ol}, K_{fb},\) and \(K_{myo}\), that are systematically identified by fitting model predictions to the data (15, 22–24) as detailed below.

Sensitivity Analysis

The sensitivity of identification of all adjustable model parameters is quantified by computing the parameter sensitivity indices, defined as the relative change in mean-squared difference in model error associated with a 10% change in parameter value. Specifically, we define the sensitivity index

\[
\theta = \frac{10}{E(p)} \left| E(P + 0.1p) - E(p) \right|
\]

where \(p\) is the estimated value of a given parameter and \(E(p)\) is minimum error associated with value \(p\). This index represents the fractional change in error relative to a fractional change in parameter value. For example a value of 1 means that a 1% change in parameter value results in a 1% change in error function.
Identification of Block 1: ATP Release and Transport

The simple model of ATP transport in blood, which is assumed to depend on flow, hematocrit, and oxyhemoglobin saturation, is identified by fitting Eq. 4 to data on venous plasma ATP at different flows, oxygen consumption rates, and hematocrit, shown in Fig. 3. Each data point represents the mean of data from 10 animals measured at one of four different experimental conditions (15): rest and three different exercise levels. Experimental data are plotted as solid circles and model predictions as solid lines. Since each data point is associated with distinct values of $H$ and $F$ as well as $S_H$ and $T_V$, there is a distinct curve in the $S_H$ vs. $T_V$ plane associated with each data point, i.e., a contour of $T_V$ vs. $S_H$ for specific fixed values of $H$ and $F$. The model predictions of $T_V$ with these distinct values of $F$ and $H$ are shown in different line/data colors. At a given value of hematocrit $H$ and flow $F$, Eq. 4 predicts that $T_V$ decreases as $S_H$ increases, as illustrated in the Fig. 3. The model also predicts that for a given level of $S_H$, $T_V$ decreases with $F$ and increases with $H$. Thus as flow increases the model predicts that the relationship between $T_V$ and $S_H$ shifts to the left.

Parameters for block 1 were estimated based on the model fits to the data illustrated in Fig. 3. The arterial plasma ATP concentration $T_A$ was estimated based on $T_V$ vs. $S_H$ data of Farias et al. (15) and was found to be close to the value reported by Farias et al. Estimated values of the parameters $J_0$, $S_0$ and $T_A$ for block 1 are reported in Table 1. The model predictions of $T_V$ are in good agreement with the data (Fig. 3A) and the model accurately describes the data on $T_V$ vs. $S_H$ at different flow and hematocrit levels (Fig. 3B).

Identification of Block 5: Effect of Sympathetic Input on Oxygen Metabolism

The effect of the sympathetic open-loop signal on myocardial oxygen metabolism ($M$) described using linear relationships between the interstitial norepinephrine concentration ($N$) is shown in Eq. 8. The parameter $K_M$ that relates $M$ to $N$ was estimated from the data of Gorman et al. (24) by least-squares fitting the straight line with slope $K_M$ and intercept $M_0$ of Eq. 8 to the data. With the intercept of Eq. 8, $M_0$ was chosen based on the control exercise data. Specifically, three different values of $K_M$ were estimated to represent the relationship between $M$ and $N$ under control condi-

Table 1. Estimated model parameters, sensitivity indexes, and constants

<table>
<thead>
<tr>
<th>Name</th>
<th>Value (Sensitivity index)</th>
<th>Units</th>
<th>Dataset Used for Identification</th>
</tr>
</thead>
<tbody>
<tr>
<td>$J_0$</td>
<td>283.388 (8.967)</td>
<td>μM/min</td>
<td>Fig. 3</td>
</tr>
<tr>
<td>$S_0$</td>
<td>0.0387 (127.72)</td>
<td>unitless</td>
<td>Fig. 3</td>
</tr>
<tr>
<td>$T_A$</td>
<td>28.151 (44.276)</td>
<td>nM</td>
<td>Fig. 3</td>
</tr>
<tr>
<td>$K_M$</td>
<td>22.767 (0.635)</td>
<td>μl O₂·min⁻¹μg⁻¹·nM⁻¹</td>
<td>Fig. 4</td>
</tr>
<tr>
<td>$M_0$</td>
<td>33.535 (0.335)</td>
<td>μl O₂·min⁻¹·g⁻¹</td>
<td>Fig. 4</td>
</tr>
<tr>
<td>$K_{nmyo}$</td>
<td>0 (0.63×10⁻³)</td>
<td>ml·min⁻¹·g⁻¹·mmHg⁻¹</td>
<td>Figs. 6 and 7</td>
</tr>
<tr>
<td>$g_0$</td>
<td>0.63×10⁻³ (0.234)</td>
<td>ml·min⁻¹·g⁻¹·mmHg⁻¹</td>
<td>Figs. 5</td>
</tr>
<tr>
<td>$K_{el}$</td>
<td>0.9797×10⁻³ (6.157)</td>
<td>ml·min⁻¹·g⁻¹·mmHg⁻¹·nM⁻¹</td>
<td>Figs. 6 and 7</td>
</tr>
<tr>
<td>$K_{db}$</td>
<td>0.3507×10⁻³ (0.394)</td>
<td>ml·min⁻¹·g⁻¹·mmHg⁻¹·nM⁻¹</td>
<td>Figs. 6 and 7</td>
</tr>
<tr>
<td>$V_c$</td>
<td>0.04</td>
<td>ml/g</td>
<td>Reeves et al. (31)</td>
</tr>
<tr>
<td>$S_A$</td>
<td>0.955</td>
<td>unitless</td>
<td></td>
</tr>
<tr>
<td>$C_o$</td>
<td>476</td>
<td>μl O₂/ml</td>
<td></td>
</tr>
</tbody>
</table>
but using a common intercept represented with a unique slope associated with that condition, receptor blockade (15, 22, 23). Each experimental condition is divided by pressure

Identification of Basal Conductance

The parameter $g_0$ in Eq. 10 is estimated by assuming that it represents the basal conductance at $M = 0$ (with no input from the open-loop and feedback pathways). Specifically, the total observed conductance (flow $F$ divided by pressure $P$) as a function of $M$ was fit with a linear relationship, as illustrated in Fig. 5. The four exercise data sets shown in the figure correspond to control conditions, and data obtained with phentolamine, with phentolamine and propranolol, and with purine receptor blockade (15, 22, 23). Each experimental condition is represented with a unique slope associated with that condition, but using a common intercept $g_0$ for all data sets.

Identification of Blocks 2, 3, 4, and 6: Open-Loop, Feedback, and Myogenic Gains

The three model parameters, $K_{th}$, $K_{ph}$, and $K_{myo}$, are estimated by fitting the output of the integrated model of Fig. 2 to data plotted in Fig. 6, as detailed below.

Figure 6, A and B, plots data on $P$ versus $M$ and $S_V$ versus $M$ obtained under control physiological conditions in awake animals during rest and exercise reported by Gorman et al. (22, 23) and Farias et al. (15). To match simulations to data (15, 22, 23) in Fig. 6B the full model was used, with pressure determined by a straight-line fit to the $P$ versus $M$ data (22, 23) in Fig. 6A: $P = (0.0001 \text{ mmHg} \cdot \mu\text{l O}_2 \cdot \text{min}^{-1} \cdot \text{g}^{-1})M + 105.41 \text{ mmHg}$. To represent these normal control conditions the model is driven by varying $N$ over the range of 0 to 15 nM, to attain values of $M$ from $M_0$ to 300 $\mu\text{l O}_2 \cdot \text{min}^{-1} \cdot \text{g}^{-1}$. To illustrate $S_V$ vs. $M$ for values of $M$ less than $M_0$, $N$ is held at 0 and $M$ varied from 0 to $M_0$.

For all simulations illustrated in Fig. 6, an average observed value of $H$ and $S_A$ over whole range of $M$ was used based on
measured values under control conditions ($H = 0.3942$ and $S_A = 0.955$). Fitting the model for all control conditions reveals the value of the $K_{myo}$ is not identifiable from the available data, because there was very little change in arterial pressure as shown in Fig. 6A, and that data are matched with $K_{myo}$ set to zero. Thus the data in Fig. 6 are effectively fit with only two adjustable parameters: the gains $K_{nl}$ and $K_{fb}$. The result that the effective gain $K_{myo}$ may be set to zero does not imply that the model predicts the absence of myogenic tone in the coronary arterioles because in the absence of myogenic tone, an increase in pressure would be expected to result in an increase in vessel lumen diameter and the effective value of $K_{myo}$ would be negative.

**Effects of $\alpha$-Adrenoceptor, $\beta$-Adrenoceptor and Purinergic Receptor Blockade**

The model was used to simulate the effects of various pharmacological agents that were used in these studies (22–24), on open-loop and feedback pathway gains. These experiments are simulated using the full integrated model, supplying pressure as a function of oxygen metabolism ($M$) determined by fitting straight-line relationships to the data, as illustrated in Fig. 7A. For phentolamine, the relationship is $P = (0.0001$ mmHg$\cdot \mu$L $O_2^{-1} \cdot min^{-1} \cdot g^{-1})M + 76.6$ mmHg; for phentolamine + propranolol $P$ was computed $P = (0.0236$ mmHg$\cdot \mu$L $O_2^{-1} \cdot min^{-1} \cdot g^{-1})M + 81.489$ mmHg; for purinergic receptor blockade, $P$ was computed $P = (0.0258$ mmHg$\cdot \mu$L $O_2^{-1} \cdot min^{-1} \cdot g^{-1})M + 119.33$ mmHg. Figure 7A shows the data and model simulations of $P$ vs. $M$ under control, phentolamine, phentolamine + propranolol and purinergic block conditions.

Model simulations were compared to data from Gorman et al. (23, 24) obtained using phentolamine to block $\alpha$-adrenoceptors, and phentolamine plus propranolol to block $\beta$-adrenoceptors that mediate the effects of adrenergic stimulation on vessel conductivity and $M$ to determine if the model can capture the observed relationship between venous oxygenation and myocardial oxygen uptake under these conditions. Similarly, the model simulation was compared to data from Gorman et al. (22) obtained with inhibitors to block the effects of the feedback pathway signal on vessel conductivity and $M$ to determine if the model can capture the observed relationship between $S_V$ and $M$ under this condition. Hematocrit ($H$) was fixed at 0.3942 for control, 0.3467 for phentolamine, 0.3537 for phentolamine plus propranolol and 0.3933 for purinergic blockade (average of reported values over whole range of $M$). Figure 7B plots the global fits of the full integrated control model to the data on $S_V$ vs. $M$ under control, as well as the data obtained following administration of phentolamine, phentolamine + propranolol and purinergic blockade.

To match the data on phentolamine and phentolamine plus propranolol the value of $K_{nl}$ was reduced compared to control, indicating that these interventions reduced the effective open-loop gain in the system. Specifically, $K_{nl}$ was reduced to 75% of its control value to match the phentolamine case and to 6.67% of its control value to match the phentolamine plus propranolol case. To match the data obtained using purinergic blockade the feedback gain $K_{fb}$ was reduced to 8.27% of its control value.

![Fig. 8. Validation of predicted venous ATP levels.](http://ajpheart.physiology.org/)

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Validation of Predicted Autoregulatory Function

The model prediction (solid line) is in reasonable agreement with the observed pressures of 104 mmHg during single pacing and 117 mmHg during paired pacing. The open-loop signal was set to zero ($K_u = 0$).

Validation of Predicted Venous ATP Levels

In estimating values of parameters associated with block 1, flow ($F$) and metabolic rate ($M$) were both fixed at experimentally estimated levels. To test the ability of the model to effectively represent the observed relationship between venous ATP and metabolic rate, predictions based on the integrated model (where $M$ and $F$ are computed as variables) are compared to measurements of venous ATP concentration ($TV$) as a function of $M$ in Fig. 8. The model simulation shows reasonable agreement to the data of Farias et al. (15).

Validation of Predicted Feedback Regulation in the Absence of Open-Loop Pathway with Cardiac Pacing

To validate the ability of the model to effectively represent the feedback pathway, a model simulation was compared to data from Yada et al. (39), in which hearts were paced in vivo under anesthetized conditions with $\beta$-adrenergic receptor blockade. Figure 9 shows measured flow ($F$) and metabolic rate ($M$) obtained during single cardiac pacing at 55 beats/min (lower $M$) and after 60 s of paired cardiac pacing at 122 beats/min. (higher $M$). To simulate this experiment the open-loop gain was set to zero ($g_{ol} = 0$). The oxygen metabolism ($M$) varied from 71 to 140 $\mu$mol O$_2$·min$^{-1}$·g$^{-1}$. Arterial pressure was varied according to $P = (0.188 \text{ mmHg} \cdot \mu\text{mol O}_2\cdot\text{min}^{-1}\cdot\text{g}^{-1})M + 90.623 \text{ mmHg}$, to match the observed pressures of 104 mmHg during single pacing and 117 mmHg during paired pacing. The open-loop signal was set to zero ($K_u = 0$).

Validation of Predicted Autoregulatory Function

Coronary resistance vessels constrict (lower hydraulic conductivity) in response to increases in arterial pressure and dilate (increase conductivity) in response to decreases in pressure (1, 29, 38). This phenomenon, termed autoregulation, contributes to the maintenance of a relatively constant flow over a range of arterial pressure. Two key physiological contributors to autoregulation are metabolic feedback and the myogenic response, both represented in the coronary control model. To test the ability of the model to capture coronary autoregulation, model predictions were compared to the data of Broten and Feigl (1), in which coronary arterial pressure was experimentally increased in anesthetized dogs under $\alpha$- and $\beta$-adrenoceptor plus cholinergic blockade.

Data from Broten and Feigl (1) on oxygen consumption rate ($M$) and flow ($F$) in response to a doubling of coronary arterial pressure are plotted in Fig. 10. The experimental conditions are simulated by assuming that the open-loop signal is zero ($g_{ol} = 0$) while using all the other parameter values from Table 1 (including $K_{myo} = 0$). The observed small increase in $M$ with increasing coronary arterial pressure ($P$) (called the Gregg effect) is accounted for in the model prediction (solid line) of the coronary flow as a function of coronary arterial pressure $P$.

Table 1. Data from Broten and Feigl (1) on oxygen consumption rate ($M$) and flow ($F$) in response to a doubling of coronary arterial pressure are plotted in Fig. 10. The experimental conditions are simulated by assuming that the open-loop signal is zero ($g_{ol} = 0$) while using all the other parameter values from Table 1 (including $K_{myo} = 0$). The observed small increase in $M$ with increasing coronary arterial pressure ($P$) (called the Gregg effect) is accounted for in the model prediction (solid line) of the coronary flow as a function of coronary arterial pressure $P$.
model by assuming a simple linear relationship: \( M = (0.045 \mu l O_2 \cdot min^{-1} \cdot g^{-1} \cdot mmHg^{-1})P + 54.1 \mu l O_2 \cdot min^{-1} \cdot g^{-1} \). Thus, here, a special case of the model was simulated with no open-loop stimulation and with \( M \) determined as an explicit function of \( P \). The model-predicted flow is compared to data from Broten and Feigl (1) in Fig. 10B. The reasonable agreement between the model prediction and the data demonstrates the ability of the model to capture the phenomenon of autoregulation.

The results shown in Fig. 10 are in agreement with the studies from Spaan’s laboratory (6, 8, 38). In the Spaan studies a step change in coronary artery pressure resulted in autoregulation of flow that was described by a mathematical model that represented a dependence on pressure and oxygen consumption rate. Interestingly, Vergroesen et al. (37) observed that the speed of coronary vascular regulation was slowed by cardiac denervation. The present simulation is based on steady-state measurements and provides no information on the speed of the response.

**Integrated Control of Coronary Blood Flow**

The model, which is able to effectively describe the relationship between coronary blood flow and myocardial oxygen consumption in vivo, can be used to probe the contributions of the various components of the model to overall flow control. The ability of the model to effectively represent the response in flow (\( F \)) to changes in exercise level is recapitulated in Fig. 11.

To illustrate the predicted relative contributions of open-loop and feedback control pathways to coronary flow \( F \), Fig. 12A shows the relative contribution to flow of each pathway as functions of exercise myocardial oxygen metabolism (\( M \)). The model predicts that under physiological conditions the open-loop, feedback pathways and basal conductance have significant contributions to total conductivity \( G \), with the relative contribution of the open-loop pathway increasing with increasing exercise and oxygen metabolism. Over the physiological range from baseline conditions (\( M = 75 \mu l O_2 \cdot min^{-1} \cdot g^{-1} \)) to maximum exercise (\( M = 250-300 \mu l O_2 \cdot min^{-1} \cdot g^{-1} \)) the variable \( g_{ol} \), which is the open-loop component of conductivity, contributes 37–67% of the sum \( G = g_{ol} + g_b + g_p + g_0 \). The relative contribution from \( g_b \) is approximately 45-30% over the observed range of exercise levels. The relative contribution from basal conductance \( g_0 \) reduces from 14 to 8% of the total conductance \( G \) as metabolism rate increases from resting to high levels.

Thus, the model predicts that under normal control physiological conditions the open-loop pathway represents a higher contribution to overall control of coronary flow than the feedback pathway when myocardial oxygen consumption is greater than \( \sim 100 \mu l O_2 \cdot min^{-1} \cdot g^{-1} \). This prediction is consistent with the relationship between venous ATP concentration and oxygen consumption rate plotted in Fig. 8. The relationship is steeper at lower oxygen consumption rates than at higher oxygen consumption rates, as the relative contribution from the
open-loop pathway is predicted to increase with increasing oxygen consumption rate (as shown in Fig. 12).

However, this prediction should not be interpreted as yielding a relative ranking of the physiological importance of these pathways. More insight into the importance of these pathways is obtained by simulating how the model behaves when these pathways are independently removed from the system. Figure 12B illustrates the ability of feedforward and feedback pathways in matching the oxygen delivery and extraction in the myocardium, from rest to exercise under control conditions, while setting \( K_{ol} = 0 \) and while setting \( K_{fb} = 0 \). Specifically, the ratio of oxygen delivery rate and oxygen utilization rate is computed and plotted as a function of \( M \). When this ratio is greater than one, there is enough flow to meet the demand. When this ratio is less than one there would not be enough flow to meet the demand, which is not sustainable during steady-state conditions. The plot illustrates how the effects of removing the feedback pathway are much more severe than those of removing the open-loop pathway. When the open loop is set to zero, \( SV \) drops compared to the control case, eliciting a response in the feedback signal. In contrast, when feedback gain is set to zero, there is no compensatory mechanism in the model. The ratio of oxygen delivery to demand becomes less than one with \( K_{fb} = 0 \), indicating the demand outpaces delivery. (The reason why the delivery is able to meet oxygen demand with \( K_{fb} = 8.27\% \) of the control level in Fig. 7 is that in addition to the simulated ATP levels increasing to overcome the block, the perfusion pressure increases during purinergic block. The model simulations in Fig. 12 are with individual gains set to zero with pressure set to the range observed under control conditions.) Although under physiological conditions the open-loop pathway contribution to conductivity is predicted to be greater than the feedback contribution, removing the feedback pathway has a more drastic effect on model behavior than removing the open-loop pathway. This is because when the open-loop pathway is removed, the feedback pathway responds to compensate for the perturbation. When the feedback pathway is removed there is, by definition, no mechanism for the open-loop pathway to sense and compensate for the associated disturbance.

The parameter \( K_{ol} \) is a quantity with dimensions of conductivity per ATP concentration that represents the amount that conductivity \( G \) increases with increasing venous plasma [ATP], \( T_v \). Similarly the open-loop gain parameter \( K_{ol} \) represents the amount that \( G \) increases with increasing interstitial norepinephrine concentration, \( N \). In contrast, the unitless physiological gain of each pathway is defined as the relative change in conductivity that is elicited by a change in the signal to each pathway. Specifically, an apparent open-loop gain may be defined

\[
A_{ol} = \frac{N}{G} \frac{\partial G}{\partial \Delta G} = \frac{N}{G} K_{ol}
\]

and the apparent feedback gain as

\[
A_{fb} = \frac{S_v}{G} \frac{\partial G}{\partial S_v} = \frac{S_v}{G} \frac{1}{F} \left[ \frac{V_H}{S_0} \frac{S_v}{F} + \frac{V_H}{S_0} \frac{S_v}{F} - \frac{V_H}{S_0} \frac{S_v}{F} \right]
\]

The values of these apparent gains for the model simulated under control conditions are plotted as function of \( M \) in Fig. 13. Near baseline resting levels of \( M \) the apparent feedback gain is approximately 1.6 meaning that a 1% decrease in \( S_v \) would result in a roughly 1.6% increase in flow. The ability of the feedback pathway to respond gradually diminishes as \( M \) is increased.

**DISCUSSION**

A mathematical model of coronary blood flow control was developed to analyze in vivo steady-state data on coronary flow and myocardial metabolism at rest and with exercise. Data from dogs at rest and graded levels of exercise and with and without specific pharmacological blockades (15, 22–24) were analyzed to estimate parameters of a control system model based on oxygen mass balance and descriptions of open-loop (feed-forward) and feedback pathways. The main findings of this study are 1) model simulations of coronary blood flow data that incorporate feedback control via adenine nucleotides and adrenergic open-loop control are consistent with canine rest and exercise data; 2) both open-loop and feedback control are important during exercise, but feedback control is essential; and 3) the model employing only feedback control gives reasonable predictions for coronary blood flow data with cardiac pacing and autoregulation without changes in the parameter values obtained from the exercise studies.

A somewhat unexpected finding is that \( \alpha \)-adrenoceptor blockade with phentolamine reduced myocardial oxygen consumption as represented in block 5 of the model and illustrated in Fig. 4. This effect has been observed earlier under resting conditions when an \( \alpha \)-adrenergic antagonist was infused into the coronary artery under resting conditions (20). This observation is also consistent with other studies that report a positive inotropic effect of \( \alpha \)-adrenergic stimulation (7, 30). These data are consistent with the interpretation that, during exercise, inhibition of metabolic rate by \( \alpha \)-adrenoceptor blockade is overridden by large increases in norepinephrine concentration.
A similar effect was found with the open-loop gain in block 4 (Fig. 2). Even though open-loop gain ($K_{ad}$) is slightly reduced by phentolamine, the open-loop conductance ($G_{ad}$) at a given oxygen metabolism ($M$) was actually increased by phentolamine due to the much higher norepinephrine concentrations. Thus, phentolamine did produce feedforward open-loop coronary vasodilatation as one would expect, as shown in Fig. 11.

The model results are consistent with the interpretation that high levels of myocardial oxygen consumption during exercise are achieved via myocardial adrenergic β-receptor activation, and there is a concomitant feed-forward high levels of myocardial oxygen consumption during exercise. Thus, phentolamine did produce feedforward open-loop coronary vasodilation due to the much higher norepinephrine concentrations.

Quantitative studies of Dankelman et al. (8, 9) suggest that the (e.g., change in heart rate and pressure). For example, the modeling studies (8, 9, 28, 38) have provided insight into the interaction of sympathetic open-loop and feedback mechanisms in the postulated adenine nucleotide-mediated pathway. The present model provides a quantitative representation of the physiology of the coronary circulation during exercise. While both open-loop control and feedback mechanisms contribute to the physiological control of coronary flow, the system is more sensitive to a disruption of the feedback pathway than an equivalent disruption of the open-loop pathway, illustrating the critical role of metabolic feedback control. In capturing the observed relationship between oxygen extraction and blood flow in the myocardium, and the effects of pharmacological inhibition of adrenergic and purinergic pathways, the model provides a quantitative representation of the physiology of the coronary circulation during exercise. While both open-loop and feedback mechanisms contribute to the physiological control of coronary flow, the system is more sensitive to a disruption of the feedback pathway than an equivalent disruption of the open-loop pathway, illustrating the critical role of metabolic feedback control.

In conclusion, a simple model, that combines adenine nucleotide (ATP, AMP)-mediated feedback control with adrenergic open-loop control, provides an understanding of how coronary flow matches myocardial oxygen metabolism. In capturing the observed relationship between oxygen extraction and blood flow in the myocardium, and the effects of pharmacological inhibition of adrenergic and purinergic pathways, the model provides a quantitative representation of the physiology of the coronary circulation during exercise. While both open-loop and feedback mechanisms contribute to the physiological control of coronary flow, the system is more sensitive to a disruption of the feedback pathway than an equivalent disruption of the open-loop pathway, illustrating the critical role of metabolic feedback control. In capturing the metabolic pathway as mediated by oxygenation-dependent ATP release from red blood cells, the model demonstrates the ability of the adenine nucleotide hypothesis to predict and explain the relevant data from cardiac pacing and autoregulation experiments.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).
REFERENCES


