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Influence of anatomical dominance and hypertension on coronary conduit arterial and microcirculatory flow patterns: a multiscale modeling study

© Jonathan P. Mynard1,2 and Joseph J. Smolich1,2
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Mynard JP, Smolich JJ. Influence of anatomical dominance and hypertension on coronary conduit arterial and microvascular flow patterns: a multiscale modeling study. Am J Physiol Heart Circ Physiol 311: H11–H23, 2016. First published May 3, 2016; doi:10.1152/ajpheart.00997.2015.—Coronary hemodynamics are known to be affected by intravascular and extravascular factors that vary regionally and transmurally between the perfusion territories of left and right coronary arteries. However, despite clinical evidence that left coronary arterial dominance portends greater cardiovascular risk, relatively little is known about the effects of left or right dominance on regional conduit arterial and microcirculatory blood flow patterns, particularly in the presence of systemic or pulmonary hypertension. We addressed this issue using a multiscale numerical model of the human coronary circulation situated in a closed-loop cardiovascular model. The coronary model represented left or right dominant anatomies and accounted for transmural and regional differences in vascular properties and extravascular compression. Regional coronary flow dynamics of the two anatomical variants were compared under normotensive conditions, raised systemic or pulmonary pressures with maintained flow demand, and after accounting for adaptations known to occur in acute and chronic hypertensive states. Key findings were that 1) right coronary arterial flow patterns were strongly influenced by dominance and systemic/pulmonary hypertension; 2) dominance had minor effects on left coronary arterial and all microvascular flow patterns (aside from mean circumflex flow); 3) although systemic hypertension favorably increased perfusion pressure, this benefit varied regionally and transmurally and was offset by increased left ventricular and septal flow demands; and 4) pulmonary hypertension had a substantial negative effect on right ventricular and septal flows, which was exacerbated by greater metabolic demands. These findings highlight the importance of interactions between coronary arterial dominance and hypertension in modulating coronary hemodynamics.

pulmonary hypertension; systemic hypertension; right coronary artery; left coronary artery

NEW & NOTEWORTHY

Using a novel multiscale model of the human coronary circulation situated in a closed-loop cardiovascular model, we performed the first comprehensive analysis of the effects of left or right coronary arterial dominance on regional conduit arterial and microvascular arterial/venous flow patterns under normotensive conditions, and with systemic or pulmonary hypertension.

IT HAS LONG BEEN KNOWN THAT blood flow in left coronary conduit arteries occurs predominantly during diastole (27, 63), when the squeezing effect of contracting myocardium on intramural blood vessels is absent (2, 68). This systolic flow impediment is less pronounced in the right coronary artery (RCA), due to a lower right ventricular (RV) cavity pressure and contractile function compared with the left ventricle (LV), with RCA flow being approximately equal in systole and diastole under normal conditions (8, 30, 40, 42, 54, 61, 77). In conjunction with these regional differences in conduit arterial flow, perfusion of the coronary microcirculation also exhibits a distinct transmural pattern, with a greater diastolic flow predominance in the subendocardium than in subepicardium, paralleling the distribution of systolic intramyocardial pressure (29, 72). Moreover, in contrast to a largely diastolic coronary arterial flow, coronary venous flow is mostly systolic (14, 43), an observation that forms the basis of the intramyocardial pump model (68).

Within the framework of these general principles, however, relatively little is known about how variations in coronary vascular anatomy and hemodynamic factors influence the balance of systolic and diastolic coronary flow in conduit arteries and intramyocardial vessels. In particular, the influence of left or right anatomical dominance on regional flow patterns is unclear. In a right dominant coronary anatomy, for example, the RCA supplies parts of the ventricular septum and LV, which may lead to greater systolic flow impediment in the RCA flow waveform compared with a left dominant anatomy in which the RCA supplies only the RV. However, aside from one published example of mostly systolic RCA flow in a nondominant RCA and mostly diastolic RCA flow in a dominant RCA (56), the effects of anatomical dominance on RCA and left coronary arterial flow patterns are largely unknown.

Systemic and pulmonary hypertension are also both likely to have significant and region-specific consequences for coronary flow patterns. Thus, systemic hypertension would raise perfusion pressures within both the left and right coronary networks, but an accompanying increase in LV systolic cavity pressure would additionally elevate intramyocardial pressure and thus counteract the increased perfusion pressure in the LV free wall (LVfw) and septum, but not the RV free wall (RVfw). By contrast, while pulmonary hypertension per se does not affect
aortic (i.e., coronary perfusion) pressure, an associated increase in RV cavity pressure might be expected to impede systolic flow to the RV myocardium and possibly the ventricular septum. Consistent with this proposition, elevated RV cavity pressure has been shown to produce RCA flow waveforms that resemble the systolic-dominant waveforms of left coronary arteries (1, 40, 73). Importantly, while chest pain is known to occur in some patients with elevated RV pressures, even in the absence of coronary obstruction (18, 38, 62), the precise mechanism underlying this problem is unclear, with current evidence conflicting as to whether these conditions cause changes in left as well as right coronary flow (23, 35, 73), while their influence on regional microcirculatory flow patterns is unknown.

In experimental and clinical settings, it may be quite difficult to unambiguously elucidate the mechanistic effects of anatomical dominance and systemic or pulmonary hypertension on coronary conduit arterial and microcirculatory flow patterns, given the presence of other potentially confounding hemodynamic factors and measurement limitations. In these settings, it is also not possible to separate direct mechanical effects of increased pressure on coronary flow patterns from effects related to the heightened flow demand that occurs with acute systemic or pulmonary arterial hypertension (12, 24), as well as the ventricular and coronary remodeling processes that occur with chronic hypertension (5, 6, 41).

Because these limitations do not apply to numerical modeling approaches, we have built on our previous work (47, 49, 51) by coupling a detailed multiscale model of the coronary circulation to a closed-loop model of the cardiovascular system that includes systemic and pulmonary hemodynamics, along with biventricular function. This coronary model accounts for wave propagation effects using anatomically based one-dimensional conduit arterial networks and also represents regional and transmural differences in blood flow patterns via multiple instances of a multilayered lumped parameter model. Within this framework, we present the first model-based comparison of coronary hemodynamics in left and right dominant anatomies and investigate the effects of systemic and pulmonary hypertension on coronary conduit arterial and microvascular flow patterns.

METHODS

Model Overview

The model consists of three main components: 1) a closed-loop model of the cardiovascular system allowing simulation of normal and pathological cardiac, valvular, systemic and/or pulmonary conditions; 2) a one-dimensional (1D) model of the major left and right conduit coronary arteries derived from measurements in humans (19, 20), allowing study of anatomical variations and wave propagation effects; and 3) a zero-dimensional (0D, or lumped parameter) model of the intramyocardial circulation, instances of which are inserted at all distal outlets of the 1D conduit artery model, enabling study of transmural and regional microcirculatory arterial and venous flow patterns. Details regarding the full formulation and numerical implementation of all model components are available in our prior studies, as summarized in Table 1, and are therefore described briefly in the following sections.

Cardiovascular Model

The closed-loop cardiovascular model (Fig. 1) is similar to that described by Mynard et al. (49) and consists of 0D compartments for the heart chambers, valves, and microvascular beds, which are connected by single 1D segments used to approximate wave propagation

![Figure 1. Schematic of the closed-loop cardiovascular model within which the coronary model was placed. Boxes represent 0-dimensional (0D) compartments (heart chambers, valves, or microvascular beds), thin connecting lines represent 0D connections, and thick connecting lines represent 1-dimensional (1D) segments. Arrows connecting heart chambers indicate chamber interactions as follows: crossed black arrows, interactions occurring between respective left and right chambers via the septum; horizontal black arrows, interactions between respective atria and ventricles caused by motion of the atrioventricular plane. Av, aortic valve; LA, left atrium; LM, left main coronary artery; LV, left ventricle; Mv, mitral valve; PA, pulmonary artery; Pv, pulmonary valve; PV, pulmonary vein; PVB, pulmonary vascular bed; RA, right atrium; RCA, right coronary artery; RV, right ventricle; SA, systemic artery; SVB, systemic vascular bed; SV, systemic vein; Tv, tricuspid valve; Vv, venous valve.](http://ajpheart.physiology.org/)
effects in the large vessel networks. The four heart chambers (LV, RV, LA, RA; Fig. 1) were each modeled as a time-varying elastance (with prescribed minimum and maximum elastance and a 2-Hill waveform shape) in series with a pressure-dependent source resistance (47, 49, 70). Interactions occurring between respective atria and ventricles caused by motion of the atrioventricular plane were represented by the Bernoulli equation, with instantaneous valve state being a continuous variable between zero (closed) and one (open), governed by the Womersley number (49) where \( w \) is heart period \( T \) and \( \mu \) is blood viscosity with a value of 0.035 poise. Wall shear stress can then be expressed as
\[
\tau_w = -\frac{2\mu q}{(1-\xi) R A} \left(1 - \xi^2\right) \frac{\partial p}{\partial x}
\]

The system of equations was completed with the following physiologically relevant power law describing the pressure-area relation (47, 48),...
where \( A_0 \) and \( c_0 \) are reference area and wave speed at a reference pressure \( p_0 \), and \( b \) is a constant for each segment, calculated via a nominal zero-area pressure of \(-10\ \text{mmHg}\) (48). External pressure \( (p_{\text{ext}}) \) was set to zero for epicardial conduit arteries, but for septal conduit arteries that lie within the contracting ventricular septum, applied \( p_{\text{ext}} \) was equal to the average of LV and RV pressures. The governing equations (Eqs. 1 and 2) were solved using a finite element method, as described in detail in Mynard and Nithiarasu (50). Conservation of flow and continuity of total pressure were assumed at junctions. Terminal 1D segments were coupled to instances of the 0D intramyocardial model supplying parts of the LVfw, RVfw, or ventricular septum (Fig. 2), as described in Mynard (47).

**Lumped Parameter Model of Intramyocardial Vessels**

The 0D model of the intramyocardial circulation (Fig. 3) is identical to that described in Mynard et al. (51), which in turn is based on the models of Bruinsma et al. (11) and Spaan et al. (69). In brief, 71 instances of the 0D model were inserted at the ends of 1D penetrating artery segments. Coupling to the 1D segments was achieved via a penetrating artery characteristic impedance \( (Z_{\text{PA}}) \) and compliance (Fig. 3), while on the venous side, penetrating vein characteristic impedance \( (Z_{\text{PV}}) \) and compliance were coupled to right atrial pressure \( (p_{\text{RA}}) \).

The intramyocardial circulation was divided into subepicardial, midwall, and subendocardial layers (Fig. 3). Following Spaan et al. (69), each layer consisted of two compartments, defined according to the compliances \( C_1 \) and \( C_2 \), approximately corresponding to the arterial and venous compartments of the layer. Each compartment contained a resistance \( (R_1 \) and \( R_2 \)) whose instantaneous value was based on a Poiseuille volume-resistance relationship (11)

\[
p - p_{\text{ext}} = \frac{2p_0c_0^2}{b} \left[ \left( \frac{A}{A_0} \right)^{b/2} - 1 \right] + p_0
\]

where \( A_0 \) and \( c_0 \) are reference area and wave speed at a reference pressure \( p_0 \), and \( b \) is a constant for each segment, calculated via a nominal zero-area pressure of \(-10\ \text{mmHg}\) (48). External pressure \( (p_{\text{ext}}) \) was set to zero for epicardial conduit arteries, but for septal conduit arteries that lie within the contracting ventricular septum, applied \( p_{\text{ext}} \) was equal to the average of LV and RV pressures. The governing equations (Eqs. 1 and 2) were solved using a finite element method, as described in detail in Mynard and Nithiarasu (50). Conservation of flow and continuity of total pressure were assumed at junctions. Terminal 1D segments were coupled to instances of the 0D intramyocardial model supplying parts of the LVfw, RVfw, or ventricular septum (Fig. 2), as described in Mynard (47).

**Parameter Estimation**

**Normotensive simulations.** Parameter values for the heart chambers and valves were identical to those used previously (52) while the venous valve parameters were as in Ref. 49. Parameters for the 1D segments and vascular beds (Table 2) were set to achieve normal values of cardiac output (6.2 l/min), mean and pulse aortic pressures (90 and 33 mmHg), mean and pulse pulmonary arterial pressures (12 and 8 mmHg) (45), along with pressure and flow waveforms with a normal appearance (52). Material properties of the 1D segments were imposed via reference wave speed \( (c_0) \). For the coronary segments, this was calculated as a function of reference radius \( (r_0) \) via

\[
c_0^2 = \frac{2}{3p} \left[ k_1 \exp(k_2r_0) + k_3 \right]
\]

where \( \alpha \) represents the damping effect of myocardial stiffness on transmission of cavity pressure in the heart wall. However, based on the conclusions of Algranati et al. (2) that the combination of CEP and SIP best accounts for available measurements, we here assume that \( \alpha = 1 \). CEP was assumed to be equal to cavity pressure on the endocardium, with a linear decline to pericardial pressure (assumed to be 0) in the epicardium; average CEP in the subendocardial, midwall, and subepicardial layers of the LV and RV free walls were therefore 5/6, 1/2, and 1/6 of the respective ventricular cavity pressures. For the ventricular septum, CEP was assumed to vary between \( p_{\text{LV}} \) and \( p_{\text{RV}} \) in a similar manner. Following Ref. 51, we assumed that SIP is directly proportional to ventricular elastance \( (E) \); for the LV free wall and septum, SIP = \( \varphi E_{LV} \); and for the RV free wall, SIP = \( \varphi E_{RV} \), where \( \varphi \) is an empirical constant.

\[
\text{CEP} = \text{SIP} \quad \text{and} \quad \text{CEP} = \text{SIP} \quad \text{when} \quad \text{CEP} = \text{SIP} \quad \text{in the epicardium; average CEP in the subendocardial, midwall, and subepicardial layers of the LV and RV free walls were therefore 5/6, 1/2, and 1/6 of the respective ventricular cavity pressures. For the ventricular septum, CEP was assumed to vary between } \text{CEP}_{LV} \text{ and } \text{CEP}_{RV} \text{ in a similar manner. Following Ref. 51, we assumed that SIP is directly proportional to ventricular elastance (E); for the LV free wall and septum, SIP = } \varphi E_{LV} \text{; and for the RV free wall, SIP = } \varphi E_{RV} \text{, where } \varphi \text{ is an empirical constant.}
\]

Following Olufsen (57), the coefficients adopted were \( k_1 = 2 \times 10^7 \text{ g s}^{-1} \text{ cm}^{-1} \), \( k_2 = -22.53 \), and \( k_3 = 8.65 \times 10^5 \text{ g s}^{-1} \text{ cm}^{-1} \) (unless otherwise stated), which produced a wave speed of 8.3 m/s in the proximal left anterior descending (LAD) artery, consistent with the value of 8.6 m/s measured in the LAD of dogs (4).

Penetrating arterial characteristic impedance \( (Z_{\text{PA}}) \) was calculated from parameters of the connecting 1D segments as \( p_{\text{PA}}/A_0 \). Next, total \( (i.e., \ combined) \ Z_{\text{PV}} \) in each major region of myocardium (i.e., LVfw, RVfw, and septum) for the left dominant model was matched to that in the right dominant model via a correction factor to avoid any differences in overall resistance distribution between models. \( Z_{\text{PV}} \) values were assumed to be half of corresponding \( Z_{\text{PA}} \) values. Total microcirculatory resistance \( (i.e., R_1 + R_{\text{PV}} + R_2) \) was then determined iteratively to achieve a target mean flow \( (2.64, 0.68, \text{ and } 1.35 \text{ ml/s}, \text{ or } 2.54, 0.66, \text{ and } 1.35 % \text{ of cardiac output, for the LVfw, RVfw, and septum, respectively.} \) This flow was distributed among regions (i.e., instances of the 0D model) in proportion to their myocardial weights, which in turn were distributed according to the inverse cube of penetrating artery radii (i.e., Murray’s law). Total weights for the
adult human LVfw, RVfw, and septum of 104, 46, and 54 g, respectively, were taken from Ref. 39. Subendocardial-to-subepicardial flow ratios (1.24 and 1.18 for LVfw and RVfw) and left-to-right septal flow ratios (1.37) were taken from Fisher et al. (21). As in Ref. 51, we assumed R1 = 1.2Rm and R2 = 0.5Rm in all myocardial regions and that 75% of Rm is dependent on the volume of chamber 1 and the remainder is dependent on chamber 2 (i.e., \( \gamma = 0.75 \) in Eq. 7).

Compliances were set to \( C_1 = 0.013 \) and \( C_2 = 0.254 \) ml/mmHg \( s^{-1} \cdot 100 \) g \(^{-1} \), and reference volumes \( V_{0,1} = 2.5 \) and \( V_{0,2} = 8.0 \) ml/100 g, both with a subendocardial-to-subepicardial (or left-to-right septal) ratio of 1.14 (11, 76). Following Ref. 51, SIP was estimated via \( q = 7 \) ml, which produced peak SIP values that were \(-18\%\) of the respective peak ventricular cavity pressures under normotensive conditions (59).

**Systemic hypertension.** Based on published data (46, 58), systemic hypertension was modeled by modifying the following input parameters (all others remaining unchanged): 1) SVB resistance increased from 1.0 to 1.65 mmHg \( s^{-1} \cdot ml^{-1} \); 2) SVB arterial compliance decreased from 1.0 to 0.5 ml/mmHg; 3) SA wave speed increased from 4.0 to 9.0 m/s to represent aortic stiffening; 4) SA proximal area increased from 6.8 to 8.5 cm\(^2\) to represent aortic enlargement (degree of tapering unchanged); and 5) pulmonary venous (PV) reference pressure (Ppv; see Table 2) increased from 6 to 10.7 mmHg. These changes raised mean SA pressure from 90 to 124 mmHg and SA pulse pressure from 33 to 96 mmHg, but caused negligible change to cardiac output. Three separate simulations of coronary flow were performed in this context. First, the purely mechanical effects of raised blood pressure were assessed, with the iterative process for determining coronary resistances repeated so that the same mean flows were achieved as for the normotensive case. Second, changes in myocardial flow demand known to occur in the setting of acute systemic hypertension were accounted for. Specifically, based on data reported by Buckberg et al. (12), blood flow to the LVfw and septum was assumed to increase in proportion to the aortic peak pressure increase (i.e., by 0.95%/mmHg, or a total of 65%). Similarly, the subendocardial-to-subepicardial flow ratio was assumed to increase by 0.17%/mmHg, or 12%. No changes were assumed for RVfw flow demand. Finally, LV and coronary remodeling occurring with chronic systemic hypertension was approximated by 1) increasing LVfw and septal mass by 65%; 2) increasing flow demand per gram of myocardium by 40%, based on data presented by Bache (5); 3) decreasing LVfw and septal intramyocardial compliance and volume per gram of myocardium by 65%, based on the observed lower capillary density with LV hypertrophy induced by pressure overload (5); and 4) decreasing the LVfw subendocardial-to-subepicardial flow ratio to 1.0 and left-to-right septal flow ratio to 1.1 (6). Note that this model does not account for all of the common secondary effects of chronic hypertension, such as changes in LV diastolic function and myocardial stiffness.

**Pulmonary hypertension.** Pulmonary hypertension was modeled as follows: 1) RV maximal elastance increased from 0.45 to 1.7 mmHg/ml; 2) PVB resistance increased from 0.05 to 0.75 ml/mmHg; 3) PVB arterial compliance decreased from 5.0 to 0.15 ml/mmHg; 4) proximal PA area increased from 7.1 to 9.6 cm\(^2\); 5) proximal PA wave speed increased from 2.5 to 4.0 m/s; and 6) area and wave speed tapering as for SA was employed, resulting in positive rather than negative wave reflection. These changes raised PA mean pressure from 12 to 60 mmHg and PA pulse pressure from 8 to 51 mmHg but caused essentially no change to cardiac output or SA pressure. Thus, importantly, simulating pulmonary hypertension involved no change to coronary perfusion pressure compared with the normotensive case. To observe the mechanical effects of raised pulmonary pressures for a given mean flow, coronary resistances were recalculated to ensure no change in mean flows or their regional or transmural distribution. As with systemic hypertension, a second simulation accounted for changes in flow demand with acute pulmonary hypertension, based on data published by Gold and Bache (24). Specifically, for the RVfw we assumed an increased flow demand of 1.1%/mmHg increase in RV peak pressure (total 78%) but no change in subendocardial-to-subepicardial flow ratio. Conversely, for the septum, we assumed no change in total flow, but a transmural redistribution, with the left-to-right flow ratio reduced from 1.37 to 0.66 (24). Chronic pulmonary hypertension was then simulated by assuming 1) a 78% increase in RV mass, similar to that reported (41) for a similar increase in peak systolic pressure; 2) a 78% increase in flow demand per gram of myocardium (41); 3) no change in RVfw subendocardial-to-subepicardial flow ratio (41), 4) a 34% increase in right septal flow and a left-to-right septal flow ratio of 1.11 (41); and 5) no change in absolute values of RVfw vascular volume and compliance, and hence a reduction of these parameters per gram of myocardium, based on the observed capillary rarefaction in pulmonary hypertension (10).

**RESULTS**

Coronary flow waveforms under normotensive conditions in left dominant (LDom) and right dominant (RDom) networks are compared in Fig. 4. Mean Cx flow was 83% higher in

![Fig. 4. Comparison of proximal LAD, Cx, and RCA flow waveforms from models representing right and left dominant anatomies under normotensive conditions. Aortic pressure and flow are shown for reference and were essentially identical in left and right dominant models.](http://ajpheart.physiology.org/)

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LDom compared with RDom, whereas mean RCA flow was 150% higher in RDom than LDom. Conversely, dominance had essentially no effect on LAD flow. The shape of the LAD and Cx flow waveforms was similar in both LDom and RDom (Fig. 5, showing mean normalized Cx waveforms) and were characterized by 1) a decrease to zero or slightly negative flow during isovolumic contraction, 2) a flow spike upon aortic valve opening, 3) a gradually decreasing plateau during mid-systole, 4) a small dip in flow toward the end of systole, 5) a large flow acceleration around the time of valve closure, and 6) sustained diastolic flow that was substantially greater than systolic flow. This flow waveform shape was also similar in proximal and distal parts of the Cx, except that the early systolic flow spike was less prominent in the distal Cx, particularly with RDom anatomy (Fig. 5).

In contrast to the Cx, the morphology of proximal and distal RCA flow waveforms differed substantially between RDom and LDom (Fig. 4). With RDom, the waveform was characterized by a large early systolic flow spike covering almost one-third of systole, whereas the flow spike was shorter with LDom. Moreover, with RDom, the level of RCA diastolic flow was substantially greater than systolic flow, whereas with LDom the level of systolic flow was slightly higher than diastolic flow. Also in contrast to the Cx, proximal and distal RCA waveforms differed substantially in RDom (Fig. 6, left), with distal RCA flow resembling the Cx waveform (i.e., greater diastolic predominance, cf. Fig. 5). On the other hand, RV branch flow (anterior marginal) was higher in systole than diastole (Fig. 6, left). Compared with RDom, which displayed significant regional variation in conduit RCA flow waveforms, the respective LDom waveforms (proximal RCA, distal RCA, and anterior marginal) were almost identical in shape (Fig. 6, right).

The effects of systemic and pulmonary hypertension on flow in the major coronary arteries are shown in Fig. 7 for an RDom anatomy (qualitatively similar differences were evident with LDom anatomy). Raising systemic pressure while maintaining flow demand had similar effects in the LAD, Cx, and RCA, namely, it 1) abolished the early systolic flow spike, 2) increased systolic flow, 3) led to a dome-like systolic flow with a prominent late-systolic descent, and 4) was associated with a more rapid flow decay during diastole. Increasing flow demand to the LVfw and septum (acute systemic hypertension) caused an increase in LAD, Cx, and RCA flows but little effect on waveform shape; similar but greater increases in total flow were observed with simulation of chronic systemic hypertension (Fig. 7, left).

Raising pulmonary pressure had differing effects on the flow waveform in these three arteries, with no effect on Cx flow, but a decrease in systolic flow and an increase in diastolic flow in the LAD and RCA. This effect was greater in the RCA, where both systolic and diastolic flow increased with simulated acute or chronic pulmonary hypertension (Fig. 7, right).
The systolic-to-diastolic flow integral ratios (S/D) for both coronary anatomies and all pressure conditions (and combinations thereof) are shown in Fig. 8. The LAD and Cx S/D were both increased by systemic hypertension, whereas the LAD displayed a decreased S/D in response to pulmonary hypertension. RCA S/D was strongly influenced by both anatomy and systemic/pulmonary hypertension, reaching as high as 1.65 with systemic hypertension and LDom and as low as 0.18 with pulmonary hypertension and RDom. Simulation of acute or chronic hypertension had a negligible effect on these flow ratios compared with the pure effects of raised pressure, except for some small to moderate effects in the dominant RCA.

Dominance had no effect on microcirculatory flow patterns, whereas systemic and pulmonary hypertension produced substantial effects, as seen in Fig. 9, which plots total arterial flow per gram of myocardium (i.e., flow across resistance R₁ in Fig. 3) to the respective transmural layers of the LVfw, RVfw, and septum. Normotensive waveforms exhibited increasing pulsatility and diastolic predominance toward the LVfw subendocardium and left layer of septum, where flow transiently became negative during isovolumic contraction, consistent with in vivo findings (43). Similar but less pronounced transmural differences were present in the RVfw. Raising systemic pressure (while maintaining total flow; Fig. 9) caused substantial increases and decreases in systolic and diastolic flow, respectively, to the RVfw, and similar but less prominent effects in the LVfw and septum, aside from the LVfw subendocardium and left septum where little change in systolic flow and a transient increase in early diastolic flow were observed. However, with increased flow demand, diastolic and systolic flow to the LVfw and septum increased. Compared with these acute hypertensive conditions, chronic hypertension decreased midwall and particularly subendocardial/left septal flow, mainly during diastole.

Raising pulmonary pressures (while maintaining flow demand) had the opposite effects on RVfw and septal arterial flow.
flow as systemic hypertension, namely, a decrease in systolic flow and an increase in diastolic flow, which were most pronounced in the subendocardium and right/midseptum. Acute and chronic pulmonary hypertension led to a relatively uniform increase in flow over the cardiac cycle in the RVfw and altered diastolic flow in the septum. On the other hand, pulmonary hypertension had no effect on LVfw arterial flow (Fig. 9).

Figure 10 shows corresponding changes in microcirculatory venous flow patterns. Under normotensive conditions, venous flow was predominantly systolic, although systolic and diastolic flows differed less in the RVfw compared with LVfw or septum, and in the RVfw subepicardium compared with subendocardium. Raising systemic pressure had a relatively minor effect on these flow patterns, while simulated acute or chronic systemic hypertension increased systolic LVfw and septal flows. Pulmonary hypertension caused a large increase in RVfw venous flow pulsatility, substantially augmenting systolic flow and suppressing diastolic flow, with flow patterns then resembling those in the LVfw (i.e., predominantly systolic). Similar but less substantial changes occurred in the right/midseptum, notwithstanding the changes in the transmural distribution associated with acute and chronic hypertension.

Figure 11 shows the total weight-corrected microcirculatory resistances for the LVfw, RVfw, and septum under all conditions tested. Anatomical dominance had no effect on the resistances. With raised systemic pressure, increased resistance was required to maintain the same flow as for the normotensive case, with relatively uniform changes across the RVfw (62–71%), but greater increases in the LVfw subepicardium (59%)/left septum (62%) compared with the LVfw subendocardium/right septum (both 27%; Fig. 11). However, with increased flow demand to the LVfw and septum in acute or chronic systemic hypertension, the required lower resistance offset the effects of increased perfusion pressure in the subepicardium, leading to similar or lower resistances (as much as 35%) compared with normotensive conditions (Fig. 11). With raised pulmonary pressure, a reduced resistance in the septum (by up to 34% in the right layer of septum) and RVfw (up to 32% in the subendocardium), but not the

Fig. 8. Effects of anatomical dominance and raised blood pressures on systolic-to-diastolic flow integral ratios in the LAD, Cx, and RCA. Superimposed narrow white bars indicate the change occurring when altered flow demand was accounted for (acute hypertension); narrow black bars indicate changes for chronic hypertension. NT, normotension; PH, pulmonary hypertension; SH, systemic hypertension.

Fig. 9. Transmural microcirculatory arterial flow patterns to the left ventricular free wall (LVfw), right ventricular free wall (RVfw), and septal (Sep) myocardium under conditions of normotension, SysHyp, or PulmHyp. Variants of hypertension simulations are 1) raised pressure with maintained flow demand (RP), 2) acute hypertension, i.e., with increased flow demand (AH), and 3) chronic hypertension (CH). Some dashed lines are not visible, since these are identical with the corresponding solid lines. Note that flow units are ml·min⁻¹·g⁻¹ of myocardium. Results for the right dominant anatomy are shown, and results for the left dominant anatomy are essentially identical.
LVfw, was required to maintain flow. Even lower resistances (50–60% of normotensive values) were required to accommodate the increased flow demand in the right septum and all layers of the RVfw with acute and chronic pulmonary hypertension (Fig. 11C).

**DISCUSSION**

This is the first modeling study to investigate the interacting effects of anatomical dominance and hypertension on coronary conduit arterial and microcirculatory flow patterns. Due to the multiscale nature of the model, we were able to show how regional conduit arterial and regional transmural flow patterns are influenced by a combination of anatomical (dominance) and hemodynamic (systemic or pulmonary hypertension, with or without altered flow demand and chronic remodeling processes) factors. The key findings of this study are that 1) RCA systolic-to-diastolic flow ratio is determined by a complex interplay between coronary anatomy, systemic arterial (i.e., perfusion) pressure, RV pressure, and flow demand, 2) aside from a change in mean Cx flow, dominance has a minor effect on the appearance of left coronary (Cx and LAD) and all microvascular flow patterns, 3) increased arterial pressure per se has a favorable effect on coronary flow due to an increased perfusion pressure, although the benefit varies regionally and transmurally and is offset by increased flow demand in the LVfw and septum, but not RVfw, and 4) pulmonary hypertension per se has a substantial negative effect on coronary flow in the RVfw and the rightmost layer of the ventricular septum, which is exacerbated by greater metabolic demands of the stressed RV.

Extending our recent work (51), the model described in this study incorporated the right coronary arterial network and placed the entire coronary model in a closed-loop cardiovascular model. Our modeling framework, which integrates global circulatory, conduit coronary arterial, and microvascular components, enables study of key phenomena that contribute to coronary flow patterns, such as ventricular, valvular, systemic, pulmonary, regional conduit arterial, and intramyocardial factors. In particular, such a model-based approach makes it possible to study these factors in isolation or in well-controlled combinations, which is generally very difficult to achieve in vivo. In our previous study (51) we showed that the model-generated coronary flow waveforms matched well with measured waveforms and could even capture subject-specific differences in sheep coronary artery flow profiles when measured aortic and left ventricular pressures and aortic flows were used as model inputs. The simulations of human coronary arteries and hemodynamic conditions in the present study produced both left and right coronary flow waveforms that were very similar to those previously measured in humans (77), captured known differences between proximal and distal measurement sites (28), and produced microcirculatory flow patterns that reflected the key features observed in vivo (43).

The potential importance of coronary anatomical dominance in relation to cardiovascular risk has been highlighted by a number of epidemiological studies. Left dominance is present in only 8–9% of the population (3, 13), but is associated with increased risk of mortality in patients with an acute coronary syndrome (25), along with nonfatal myocardial infarction and all-cause mortality in patients with coronary artery disease (74,
Suggestively, the prevalence of right dominance in the general population has been shown to increase with age (34). Although our study does not provide direct insight into the mechanisms underlying the increased risk associated with left dominance, the predicted 83% higher Cx flow in left than right dominance highlights the substantially increased dependence of myocardial perfusion on the Cx with left dominance, implying greater vulnerability in the setting of left main or Cx obstruction.

Aside from differences in mean flow to Cx and RCA, we showed that dominance is a major determinant of the phasic RCA flow waveform. The greater systolic flow impediment in the dominant vs. nondominant RCA arises from differences in the relative supply of blood flow to the right ventricle (which experiences little systolic flow impediment) and parts of the left ventricle and septum (which experience substantial systolic flow impediment), as demonstrated in Fig. 6. By contrast, although dominance affected mean Cx flow, it had a minor influence on the waveform shape, given that both the dominant and nondominant Cx exclusively supply myocardium that experiences similar degrees of systolic flow impediment (Fig. 5). Dominance per se was also predicted to have a negligible influence on microcirculatory flow patterns, which is due to the majority of vascular resistance residing in the small intramyocardial vessels. Note, however, that, in the setting of diffuse coronary atherosclerosis, significant resistance may also reside in the epicardial arteries (17), and dominance may then influence myocardial perfusion patterns.

Systemic hypertension has complex consequences for coronary flow. On the one hand, systolic perfusion pressure is increased, which favors forward flow, but on the other hand, LV cavity pressure is also high and impedes coronary flow via an increased intramyocardial pressure. Our simulations suggested that a raised perfusion pressure “wins out” over the increased intramyocardial pressure, with an increased resistance being required to maintain the same level of flow as normotensive conditions (Fig. 11B). This would appear to be related to the finding that LV cavity pressure most strongly affects the innermost layer of myocardium (29, 31, 66, 67), noting that the greatest resistance increase required to maintain normotensive flow levels was in the midwall and subepicardial/right septal layers. However, the positive effects of raised systemic pressures per se were overcome by the increased flow demand occurring with high LV pressures in the setting of acute or chronic hypertension (12), such that vasodilation was still required in the midwall and subendocardium of the LVfw and septum despite the increased perfusion pressure (Fig. 11B). On the other hand, in the RVfw, LV cavity pressure had no direct effect on intramyocardial pressure or metabolic demands, and hence the favorable effect of perfusion pressure was unencumbered. In addition, the high systolic perfusion pressure led to an increase in the systolic-to-diastolic flow ratio (Fig. 8), consistent with prior experimental data (16, 60).

A number of previous studies have investigated the effects of increased pulmonary pressures on right coronary flow. Both acute and chronic experiments of raised RV pressure in dogs
(22, 40) led to a decreased S/D in the RCA, a finding that was recently also found in patients with pulmonary hypertension (73). Interestingly, Akasaka et al. (1) did not detect this difference in the RCA of their patient group, although S/D was decreased in a right ventricular branch. Conflicting data exist as to the effects of increased RV pressure on left coronary flow. Chilian and Marcus (15) found no effect on LAD flow in dogs with acute RV hypertension, and Van Wofleren et al. (73) reported an increased mean LAD flow in patients with pulmonary hypertension vs. controls, whereas Koskenvuo et al. (35) reported a decrease in LAD flow in an experimental model of pulmonary hypertension. However, findings of the latter study, along with earlier experimental studies of RCA flow (22, 40), may have been confounded by a concomitant fall in aortic blood pressure.

In our modeling study, we were able to test the effects of RV pressure on coronary flow independent of changes in aortic pressure or other secondary responses to pulmonary hypertension, such as changes in flow demand due to increased RV mass and increased oxygen consumption (22, 73). Consistent with previous work (22, 40, 73), our simulations predicted that increased RV pressure causes a pronounced fall in S/D in the RCA, along with a moderate increase in the LAD and a small decrease in the dominant CX, which supply part of the septum (Fig. 8). These changes were due to dramatic decreases in systolic RVfw subendocardial flow and abolition or reversal of systolic right/midseptal flow (Fig. 9); this was clearly caused by an augmented intramyocardial pump effect, given the accompanying increase in systolic venous flows (Fig. 10). Importantly, while microvascular resistance in these regions had to decrease by ~30% for mean flow to be maintained, further reductions were needed (50–60%) to satisfy the increased flow demand caused by raised metabolic needs in the context of acute or chronic pulmonary hypertension. This implies a reduced vasodilatory reserve capacity in these regions, as has been suggested by experimental and clinical studies (5, 26, 73).

A central finding of our study was that RCA flow patterns are determined not only by RV pressure but by a combination of anatomical and systemic and pulmonary hemodynamic factors. In particular, left dominance raised S/D compared with right dominance, whereas systemic hypertension raised S/D and pulmonary hypertension decreased S/D compared with normotension. These findings suggest that the S/D ratio is unlikely to be a reliable indicator of pulmonary hypertension severity unless perhaps anatomy and systemic pressures are accounted for. For example, as depicted in Fig. 8, left dominance with (severe) pulmonary hypertension may produce the same S/D as normotension with right dominance. Similarly, a decreased S/D with pulmonary hypertension may be offset by raised systemic arterial pressures.

Our study had a number of limitations. We tested representative left and right dominant coronary anatomies but did not investigate the spectrum of individual variability, such as balanced or small RCA dominant anatomies; however, LDom and RDom are the two extremes. In the future, it may be of interest to adapt the 1D network model to patient-specific anatomy based on three-dimensional CT angiography. In all cases, we assumed no change in the ratio of S/D to ventricular elastance (ϕ); while this may change in reality due to increased wall stress or altered myocardial contractility occurring with hypertension, we previously showed that an increase in SIP simply increases systolic flow impedance (51).

The main effects of chronic hypertension reported in experimental studies were accounted for in our study, including altered flow demand, transmural flow distributions, and reduced compliance/volume per gram of myocardium. However, we did not account for other changes that commonly occur with chronic systemic hypertension, such as impaired LV relaxation, reduced LV passive compliance, epicardial vessel remodeling and/or arteriosclerosis, the effects of increased myocardial stiffness on myocardium-coronary interactions, or complex geometrical and mechanical changes such as alterations in regional cardiac deformation (23). Detailed study of these processes is beyond the scope of the current work but warrants investigation in future studies. However, the observed agreement between our simulations and available in vivo data suggests that we have captured the major phenomena contributing to altered coronary flow patterns in hypertension. For example, Ohtsuka et al. (55) found that the LAD diastolic flow fraction in patients with systemic isolated systolic hypertension was lower than in normal subjects (0.71 ± 0.06 vs. 0.81 ± 0.08); our model-predicted flow fractions were 0.74 and 0.84, respectively. Simulated changes in the coronary flow waveform with acute or chronic hypertension, compared with normotension, were also very similar to changes observed in vivo (15, 33, 40, 55, 73).

In summary, we have presented a powerful multiscale modeling framework for studying a broad range of anatomical and hemodynamic factors that influence coronary flow dynamics. In the present study, we applied this model to study the determinants of regional coronary conduit arterial flow patterns and microcirculatory flow patterns. Our findings suggest that interactions between coronary arterial dominance and systemic or pulmonary hypertension have significant region-specific effects on these flow patterns. These effects should be considered when interpreting clinical or experimental coronary blood flow data.

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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS
J.P.M. and J.J.S. conception and design of research; J.P.M. performed experiments; J.P.M. analyzed data; J.P.M. and J.J.S. interpreted results of experiments; J.P.M. prepared figures; J.P.M. drafted manuscript; J.P.M. and J.J.S. edited and revised manuscript; J.P.M. and J.J.S. approved final version of manuscript.

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