Online Supplements: Expanded Methods

Coronary flow (Fig. 2B) was analyzed (1) subject to prescribed boundary conditions (Fig. 2E; Table 1) and myocardium/vessel interaction (Eq. 3; Fig. 2D). To that end, the network anatomy has been reconstructed (Fig. 2A) from morphometric data (14 -16); and a vessel-in-myocardium micromechanical sub-model (1) was used to describe the *in-situ* vessel compliance (Eq.2; Fig. 2C).

I. Anatomic Reconstruction

Reconstruction relied on the morphometric data (14-16) and consisted of two stages: reconstruction of microvascular networks, followed by integration into a transmural coronary network.

Microvascular networks were reconstructed in an iterative manner, relying on data-based (14-16) vessel lengths, connectivity, and capillary branching pattern, and subject to two constraints: i) the measured (14) distance between arteriolar and venous domains and ii) the ratio between arteriolar and venous segments (14). Initially, one arteriole and two venules were located 510 μm apart. They were assigned order 1 and order -1, respectively (15, 16). Then, arterial and venous capillaries (14) were attached to these corresponding vessels, according to connectivity data (15, 16). Vessels lengths were assigned according to the measured statistical data (14-16). Additional connecting and cross-connecting capillaries were connected to these capillaries according to branching patterns statistics (14). Finally, additional arterioles and venules were connected to the previously posed respective vessels, thus increasing the orders of the input and output vessels. This process was iterated until capillaries bridged the gaps between arteriolar and venous domains, resulting in a network of 174 micro-vessels (Fig. 2A) fed by one order 3 arteriole and two order –3 venules. The network capillary density is roughly 2800 capillaries/mm^2, consistent with measured data (3, 21). A student T-test showed (1) no statistically-significant differences between the data and reconstructed network.

Integration into a coronary network: To reduce the computational load associated with a full-scale network (13) but still retain realistic morphometric features, reconstructed microvascular networks were placed at representative transmural locations, depending on the assumed anatomy (see methods). The basic configuration assumes transmurally homogeneous vessels density. Hence, microvascular networks were evenly placed at subepicardium (Myocardial Relative Depth, *MRD*=0.125), midwall (*MRD*=0.325 and MRD=0.625) and subendocardium (*MRD*=0.875). In contrary, to simulate twice higher subendocardial vessel density, each

microvascular network placed at subepicardium was matched by two subendocardial microvascular networks.

All microvascular networks were interconnected via intramyocardial arterial and venous tree-like networks and linked with the major epicardial vessels. The latter networks, taken to be symmetric and dichotomous, were reconstructed based on the morphometric data (15, 16), but assigned identical daughter vessels diameters, lengths and outlet flow conditions at each bifurcation. The *MRD* of interconnecting vessels was assigned intermediate values, depending on their transmural location. The symmetric arterial tree most proximal artery was chosen to be of order 8, since these arteries are the first to penetrate the cardiac wall (13). The number of generations arising from this artery, and the order of each segment in the arterial tree were assigned based on connectivity and segment-to-element data (16). The order of the most distal vessels in the arterial tree was set to 4, thus matching the order of the reconstructed microvascular inlet arteriole. The length of each segment in the tree was assigned to fit the statistical data (16), while maintaining monotonic reduction of diameters along the element. The venous tree was reconstructed in a similar manner. The reconstructed network has 906 segments, representing the flow in characteristic myocardial layers.

II. Flow Simulation:

Flow in each vessel was analyzed using a three-element Windkessel model consisting of two identical non-linear resistors and one non-linear capacitor (Fig. 2B). This lumped segment flow model was previously validated (12) against a distributive (5) model of a coronary vessel. At each network bifurcation, mass conservation implies that the sum of discharges Q^{jk} should vanish, i.e.:

$$\sum_{j=1}^{3} Q^{jk} = \sum_{j=1}^{3} \frac{P_{IV}^{j} - P_{bif}{}^{k}}{\Re^{j}/2} = 0 \quad k = 1, 2..., \textit{Bifurcation No.} \tag{S1}$$

Here P_{IV}^{j} denotes the intravascular pressure in each of the 3 vessels composing the k^{th} bifurcation, and $P_{bif}{}^{k}$ is the bifurcation pressure. The resistance of each vessel *n* ($\Re^{n}$) is calculated from Poiseuille's law, i.e.:

$$\Re^{n}(t) \equiv \frac{Q^{n}(t)}{P_{in}{}^{n}(t) - P_{out}{}^{n}(t)} = \frac{128\mu^{n}(t)L^{n}}{\pi D^{n}(t)^{4}} \tag{S2}$$

where P_{in}^{n} and P_{out}^{n} denote vessel inlet and outlet pressures, respectively. *L, D* and μ are the vessel length, diameter and blood apparent viscosity, respectively. Vessel diameter D varies during the

cardiac cycle due to the time-varying intravascular and extravascular (Eq. 3) pressures, according to vessel *in-situ* compliance (Eq. 2). Viscosity was taken to vary with diameter and hematocrit (Table 1), following Pries et al. (20). Hence both vessel and network resistances are highly non-linear.

Conservation of mass requires that the difference between vessel in and out discharges (Q^n_{in} and Q^n_{out}, respectively) should equal the time-derivative of the vessel's volume (V^n), i.e.:

$$Q^n_{in}(t) - Q^n_{out}(t) = \frac{P^n_{in}(t) - P^n_{IV}(t)}{\Re^n(t)/2} + \frac{P^n_{out}(t) - P^n_{IV}(t)}{\Re^n(t)/2} = \frac{dV^n}{dt} = \frac{d}{dt}\left(\frac{\pi D^2(t) L}{4}\right)^n \qquad \text{(S3)}$$

Computational Scheme: Since each bifurcation-pressure P_{bif} equals either P_{in} or P_{out} of the vessels forming that bifurcation, Eqs. S1-S3 can be combined, resulting in a system of N non-linear ordinary differential equations (N denotes the number of network vessels), which was iteratively solved using the MATLAB® ode15s solver until satisfying periodicity condition. This was fulfilled using the shooting method, i.e., after an initial guess of the intravascular pressure in each vessel, the numerical scheme was carried out for several cardiac cycles until solutions at consecutive cycles converged to within preset tolerance. This tolerance was set as follows: the maximum allowed pressure difference (at any of the vessels) between the beginning and the end of a cardiac cycle should be <0.1 mmHg. Numerical accuracy of the final solution was ascertained based on the criteria that the maximum difference between total flows into the feeding artery and out of its draining vein during a cardiac cycle was <5% of the total inflow.

***Boundary Conditions*:** were adopted from measured data rather than being evaluated from a combined heart-vessel model, in view of inevitable approximations required in such a complex model and the likewise inevitable need to adjust the model parameters to fit the data.

Inlet, Outlet and Left Ventricle Pressures: P_A(t), P_V(t) and LVP(t) respectively, were taken from Hurst & Logue (11). The signals were modified for a specific heart rate (Table 1) by changing the diastolic time fraction (*DTF*, the period from minimal to maximal time derivative of *LVP* divided by the cardiac period(6)) taken from measured data (6). The signals amplitudes were scaled according to the values listed in Table 1.

*Sarcomere Stretch Ratio (*SSR*),* required for quantification of intra-myocyte pressure (Eq. 3), has been observed to be highly coupled to ventricular volume (1). Thus, the ventricular volume waveform (11) was used for the *SSR* waveform, subject to 5% elongation from early to end diastole, and 16% shortening from end-diastole to end-systole.

III. In-situ Vessel Compliance-The Vessel-in-Myocardium Micromechanical Sub-Model

Solution of Eq. S1-S3 requires calculation of the instantaneous (pressure-dependent) diameter in each vessel through Eq. 2. The diameter-pressure curves described by Eq. 2 were thus obtained for each vessel separately by calculating (1), through a vessel-in myocardium sub-model (Fig. 2C), the lumen diameter under prescribed trans-luminal pressures ΔP. This calculation based on vessel morphometry (4, 14-16), using a detailed micro-mechanical stress analysis. A simplified (22) geometry of two concentric cylinders was considered: each vessel is surrounded by a myocardial tissue of circular cross-section. The myocardial outer diameter was taken to satisfy the measured 1:7 vessel-to-myocardium area ratio (2, 21). Both tissues are considered incompressible and hyperelastic (see below), having common interface. Calculation of the pressurized (loaded) lumen diameter requires the stress free (reference) configuration of vessel and of myocardium. Hence, the vessel-in-myocardium model equations presented below were initially solved at several loading configurations to determine the (unknown) stress free configurations.

Model Equations: *Kinematics:* The axi-symmetric mappings between each pair of configurations (see below) *i* and *i+1* in cylindrical coordinates is $(r,\theta,z)_i \rightarrow (r,\theta,z)_{i+1}$ prescribed by:

$$r_{i+1} = r_{i+1}(r_i); \quad \theta_{i+1} = (OA_{i+1} / OA_i) \cdot \theta_i; \quad z_{i+1} = \Lambda_{i+1,i} \cdot z_i \tag{S4}$$

where OA denotes the cylinder opening angle, L is its length and the stretch ratio $\Lambda_{i+1,i} = L_{i+1} / L_i$. Incompressibility implies that:

$$r_{i+1} = \sqrt{\left(r_{i+1}^{in}\right)^2 + \left[\left(r_i\right)^2 - \left(r_i^{in}\right)^2\right] \cdot (OA_i / OA_{i+1}) / \Lambda_{i+1,i}} \tag{S5}$$

The Green-Lagrange strain is $\mathbf{E} = (\mathbf{F}^T\mathbf{F} - \mathbf{I}) / 2$ where $\mathbf{I}$ is unit matrix and $\mathbf{F}$ - the deformation gradient for each mapping between configurations. Assuming no twist, $\mathbf{F}$ is given by:

$$\mathbf{F} = diag\,(\partial r_{i+1} / \partial r_i \quad \Lambda_{i+1,i} \cdot OA_{i+1} / OA_i \quad \Lambda_{i+1,i}) \tag{S6}$$

Explicit expressions for the deformation gradient of each mapping are given below.

Equilibrium Equations: The Cauchy stress tensor $\mathbf{T}$ is derived from the strain energy function W of each material (vessel wall and myocardium, see below) via the hyperelastic relationship $\mathbf{T} = -P\mathbf{I} + \mathbf{F} \cdot (\partial W / \partial \mathbf{E}) \cdot \mathbf{F}^T$. The equilibrium equations in the circumferential and axial directions imply that the Cauchy stress components $T_{r\theta}$ and T_{rz} vanish. The radial force equilibrium equation is $\partial T_{rr} / \partial r + (T_{rr} - T_{\theta\theta}) / r = 0$. By applying the axial and radial

equilibrium equations, the external axial force F_z and the trans-luminal pressure ΔP can be expressed in terms of the components T_{ij} of the tissue stress tensor **T** as follows (10):

$$F_z = \pi \int_{r_{in}}^{r_{out}} \left(2T_{zz} - T_{rr} - T_{\theta\theta}\right) r dr; \qquad \Delta P = \int_{r_{in}}^{r_{out}} \frac{T_{\theta\theta} - T_{rr}}{r} dr \tag{S7}$$

The Reference Configuration: The available data consists of statistics of the *in-situ* diameter, length and wall thickness (4, 14-16) taken under fixed intravascular pressure (*vessel cast configuration*). The data however, do not account for transmural morphometric heterogeneity. Under the assumption of larger subendocardial vessels (see methods), the reconstructed diameters were first modified by up to ±10% from the vessel cast values in a linear transmural manner. To obtain the reference configurations, the vessel/myocardium equilibrium equations (Eqs. S7) were solved subject to the relevant mappings and loading boundary conditions. The latter are:

(i) *The Cast Configuration:* Kassab and co-workers (4, 14-16) diameters were measured under fixed cast pressure. The loading conditions in this configuration are $\Delta P^v + \Delta P^m = \textit{casting pressure}$ .where v and m superscripts denote the vessel and myocardium, respectively. Each vessel's specific cast pressure was taken from a steady state coronary flow analysis (19) based also on Kassab data.

(ii) The *Unloaded Configuration:* The transition to this configuration is prescribed by the mapping from the cast configuration. The loading conditions here are $F_z^v + F_z^m = 0; \quad \Delta P^v + \Delta P^m = 0$. Based on previous data (7) the axial stretch was taken to remain constant during this mapping.

(iii) *The Un-tethered Configuration:* Unloaded coronary vessels are not stress-free. When myocardial tethering is removed, large epicardial arteries were found to shorten by 0% in human ex-vivo (9) and 30% in swine (23) (i.e., vessels' tethering stretch ranges between 1.0 and 1.4, Table 1). The un-tethered configuration was obtained upon mapping from the tethered unloaded configuration. The loading conditions in this un-tethered state are $F_z^v = 0; \quad F_z^m = 0; \quad \Delta P^v + \Delta P^m = 0$ where it is assumed that the two cylinders maintain a common but stress-free interface.

(iv) *The Stress-Free (Reference) Configuration:* The tethered-free vessel and myocardium are still not stress-free, but rather loaded by internal residual stress. Their magnitudes are quantified by the measured OA of the corresponding cylinders when cut open. For coronary vessels, OA are specimen dependent. For the myocardium OA = 2.75 rad. (17).

158 The stress-free reference configuration is obtained by mapping between configurations A and D.
159 *The deformation gradient tensor:* The deformation gradient $\boldsymbol{F}$ is determined by the mapping of
160 coordinates between two loading configurations. Specifically, the transition from stress-free (*sf*
161 subscript) to un-tethered (*unt*), un-tethered to unloaded (*unld*), and unloaded to loaded
162 configurations, combined with tissue incompressibility, leads to:
163

$$F_{sf\to unt}^{v/m} = diag\left(\frac{OA^{v/m} r_{sf}^{v/m,in}}{\pi r_{unt}^{v/m,in} \Lambda_{unt,sf}^{v/m}}, \frac{\pi r_{unt}^{v/m,in}}{OA^{v/m} r_{sf}^{v/m,in}}, \Lambda_{unt,sf}^{v/m}\right)$$

$$F_{unt\to unld}^{v/m} = diag\left(\frac{r_{unt}^{v/m,in}}{r_{unld}^{v/m,in} \Lambda_{unld,unt}^{v/m}}, \frac{r_{unld}^{v/m,in}}{r_{unt}^{v/m,in}}, \Lambda_{unld,unt}^{v/m}\right) \quad \text{(S8)}$$

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$$F_{unld\to load}^{v/m} = diag\left(\frac{r_{unld}^{v/m,in}}{r_{load}^{v/m,in} \Lambda_{load,unld}^{v/m}}, \frac{r_{load}^{v/m,in}}{r_{unld}^{v/m,in}}, \Lambda_{load,unld}^{v/m}\right)$$

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166
167 Here the superscript v/m denotes the specific cylinder: either vessel wall (v) or myocardium (m),
168 r^{in} is the cylinder internal radius, and Λ is the axial stretch. The effect of dynamic axial stretch
169 was previously (1) shown to have small effect on the predicted results and was thus not accounted
170 for.
171 ***Vessel and Myocardium Constitutive Properties:*** The description of the multiaxial material laws
172 of vessel wall (23) and of the myocardium (18) are based on Fung-type pseudostrain energy
173 functions:

$$W = \frac{C_1}{2}\left(\exp(Q) - 1\right)$$

$$Q^v = C_2^v E_{\Theta\Theta}^2 + C_3^v E_{ZZ}^2 + C_4^v E_{RR}^2 + 2\left(C_5^v E_{\Theta\Theta} E_{ZZ} + C_6^v E_{ZZ} E_{RR} + C_7^v E_{\Theta\Theta} E_{RR}\right) \quad \text{(S9)}$$

174

$$Q^m = C_2^m (I_1 - 3)^2 + C_3^m (I_1 - 3)(I_4 - 1) + C_4^m (I_4 - 1)^2$$

175 Here I_1 and I_4 are the first and fourth strain invariants respectively, and E_{ii} are the components of
176 the Green-Lagrange strain tensor.
177 The parameters C were previously estimated for 10 vessel samples (23) and 7 myocardial samples
178 (18). To obtain a representative vessel/myocardium pair, each of the 10 vessel parameter sets (23)
179 was combined with each of the 7 parameter sets of the passive myocardial samples (18), and
180 properties of each of the vessel/myocardium pairs was used as inputs to evaluate the four

parameter of Eq. 2. The pair having the best fit to the *in-situ* data of swine large coronary arteries (8) (Fig. 2C) was used for flow analysis.

Computational scheme: To derive the stress-free configuration from the vessel cast (input) one, the internal and external radii of both cylinders (vessel wall and myocardium) at the three unknown configurations (unloaded, un-tethered and stress-free) are required. In addition to these 12 unknowns, 3 axial stretches need to be determined: the stretches of both vessel wall and myocardium due to closure of the opening angle ($\Lambda^{v}_{unt,sf}$ and $\Lambda^{m}_{unt,sf}$, respectively), and the myocardium stretch due to tethering, $\Lambda^{m}_{unld,unt}$. The vessels' tethering stretch $\Lambda^{v}_{unld,unt}$ (Table 1), is a measured input. Hence the total number of unknowns is 15.

The cast internal and external radii are known from the data. Hence, in each unknown configuration and for each tissue (vessel and myocardium), for each given internal radius the incompressibility condition (Eq. S5) yields the corresponding external one. Additionally, the assumption of common interface between cylinders at each of the above three configurations eliminates three more unknowns. Thus the number of unknowns is reduced from 15 to 6 (i.e., the vessel internal radii in stress-free, un-tethered and unloaded configurations; $r^{v,in}_{sf}$, $r^{v,in}_{unt}$ and $r^{v,in}_{unld}$, respectively, and the three unknown axial stretches listed above).

The six unknowns were calculated by applying the vessel-in-myocardium model equations under the six loading boundary conditions listed above (one in section i, two in ii and three in iii). The solution of this highly non-linear system was obtained by MATLAB® ga code for genetic algorithm search and MATLAB® fsolve.

With the stress-free configuration determined, the vasodilated vessel diameters were evaluated (using the above MATLAB® codes) to optimally satisfy force equilibrium (Eqs. S7), subject to the vessel transvascular pressure. These values were presented as surfaces of $D = D(D_{cast}, \Delta P)$ for 3 vessel types: arteries, capillaries, and vein. Based on the experimental results of Hamza et al. (8), the above response surfaces were fitted for each vessel by a sigmoid function (Eq. 2).The maximum and mean errors associated with this fit relative to the exact solution was found to be 6% and <1%, respectively in all vessels under all simulated loading conditions.

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