Supplemental Material

Myocardial perfusion and flow reserve in the asynchronous heart: mechanistic insight from a computational model

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1. Detailed Methods

1.1 Model of myofiber mechanics

The contraction model currently used in CircAdapt is a modified Hill model based upon the one presented by Lumens et al [1]. The model aims to reproduce basic properties of length-dependent activation in cardiac tissue [2,3]. The fiber stress is determined by the rise of contractility in the fiber (representing density of cross bridge formation) and the fiber strain. The fiber model is divided into an active and passive stress component, with the active stress arising from myofiber contraction, and the passive stress component arising from the soft tissue deformation of the myocardium.

Natural myofiber strain (ε_f) was converted to sarcomere length (L_s) by

$$L_s = L_{s,ref}\, e^{\varepsilon_f} \tag{S1}$$

with $L_{s,ref}$ the reference sarcomere length at zero myocardial strain.

Active fiber stress

The active fiber stress is determined by a modified Hill model controlled by two state variables, the contractile element length L_{sc} and contractility C. The latter parameter is physiologically related to intracellular calcium concentration. The time derivative of L_{sc} depends linearly on length of the series elastic element ($L_s - L_{sc}$) and equals zero for isometric contraction:

$$\frac{dL_{sc}}{dt} = v_{max}\left(\frac{L_s - L_{sc}}{L_{se,iso}} - 1\right) \tag{S2}$$

where v_{max} represents velocity of sarcomere shortening with zero load and $L_{se,iso}$ length of the isometrically stressed series elastic element. Dependence on v_{max} represents the myofiber force-velocity relation so that shortening velocity increases with applied external force.

Contractility is a phenomenological parameter representing the density of cross bridge formation within the fibers and is determined by the following differential equation:

$$\frac{dC}{dt} = \frac{1}{\tau_R} \cdot C_L(L_{sc}) \cdot F_{rise}(t) + \frac{1}{\tau_D} \cdot C \cdot g(X) \tag{S3}$$

where,

$$\tau_R = 0.55\, T_r\, t_A \tag{S4}$$

$$\tau_D = 0.33\, T_d\, t_A \tag{S5}$$

T_r and T_d are constants, and t_A is the duration of activation of the fiber, which depends on the sarcomere extension:

$$t_A = 0.65 + 1.057 \frac{L_{sc}}{L_{sc0}} \tag{S6}$$

where L_{sc0} represents contractile element length with zero load.

C_L describes the increase in cross bridge formation with intrinsic sarcomere length due to an increase in available binding sites:

$$C_L(L_{sc}) = \tanh(4.0(L_{sc} - L_{sc0})^2) \tag{S7}$$

F_{rise} is a phenomenological representation of the rate of cross bridge formation within the patch:

$$F_{rise}(t) = 0.02 \cdot x^3(8 - x)^2 e^{-x} \tag{S8}$$

$$x = \min\left(8, max\left(0, \frac{t_c}{\tau_R}\right)\right) \tag{S9}$$

$$t_c = t - t_{act} \tag{S10}$$

with t_{act} the time of onset of activation.

The term $g(X)$ is an approximation of the function tanh(x) using a sine curve to ensure that it takes value 0 or 1 outside the region where it exhibits a large change:

$$tanhx = 0.0 + 0.5 \cdot \sin\left(sign\left(\frac{t_c - t_A}{\tau_D}\right) \cdot min\left(\frac{\pi}{2}, abs\left(\frac{t_c - t_A}{\tau_D}\right)\right)\right) \tag{S11}$$

The effect of the formulation for contractility is as follows: as the chamber wall is stretched by an expanding volume of blood, the series elastic element (L_{se}) lengthens, causing a corresponding lengthening of the contractile element (L_{sc}). Given an onset of cross bridge formation in response to electrical excitation at time t_{act}, the contractility C begins to rise according to $F_{rise}(t)$. The longer the contractile element L_{sc}, the greater both the duration of the contractile phase (equation (S6)) and the rate of increase in contractility (equation (S7)) are. Once the duration of activation, t_{act}, is over, the contractility begins to decay exponentially.

Active myofiber stress $\sigma_{f,act}$ depends on contractility and sarcomere length:

$$\sigma_{f,act} = \sigma_{act} \cdot C \cdot (L_{sc} - L_{sc0}) \cdot \frac{L_s - L_{sc}}{L_{se,iso}} \tag{S12}$$

where σ_{act} is a parameter scaling the tissue's ability to generate stress.

Passive fiber stress

Passive deformation of the soft tissue making up the myocardium will generate a passive stress ($\sigma_{f,pas}$) within the walls. This contains two components, the stress arising from the myocytes themselves due to internal structures such as titin anchoring to the Z disc ($\sigma_{f,tit}$), and the stress arising from the extracellular matrix surrounding the myocytes ($\sigma_{f,ECM}$).

$$\sigma_{f,pas} = \sigma_{f,tit} + \sigma_{f,ECM} \tag{S13}$$

The extension of the cells for the passive stress calculation is done relative to a different reference length $L_{s0,pas}$ as follows:

$$L_{s,pas} = \frac{L_{s,ref}}{L_{s0,pas}} e^{\varepsilon_f} \tag{S14}$$

The passive stress due to cellular structures such as titin is governed by the following equation:

$$\sigma_{f,tit} = 0.01\, \sigma_{act}\left(L_{s,pas}^{k} - 1\right) \tag{S15}$$

$$k = \frac{2L_{s,ref}}{dL_{s0,pas}} \tag{S16}$$

The ECM is modelled as being stiffer than the contribution due to cellular structures such as titin:

$$\sigma_{f,ECM} = 0.0349\, \sigma_{pas}\left(L_{s,pas}^{10} - 1\right) \tag{S17}$$

where σ_{pas} is a parameter scaling the passive myofiber stress.

Total fiber stress

Total Cauchy myofiber stress σ_f is the sum of active and passive stress:

$$\sigma_f\left(\varepsilon_f\right) = \sigma_{f,pas} + \sigma_{f,act} \tag{S18}$$

1.2 Calculation of regional demand

The calculations of regional myocardial oxygen demand used in this study are based on a study by Delhaas *et al.* [4]. Regional oxygen demand is assumed to be proportional to the regional fiber stress-strain area (SSA), with the latter being a summation of regional potential energy (PE) and regional external work (EW).

$$SSA = PE + EW \tag{S19}$$

Potential energy

The volume of blood in the cavity is used to derive the area A_m of the mid-wall surface on which wall tension T_m is calculated [1]. Under the assumption that mid-wall area A_m is proportional to the square of sarcomere length L_s and that no stress can be developed at estimate sarcomere length $L_{s,0}$ at zero transmural pressure, $L_{s,0}$ can be related to $A_{m,0}$ as follows

$$A_{m,0} = \left(\frac{L_{s,0}}{L_{s,ref}}\right)^2 \cdot A_{m,ref} \quad \text{(S20)}$$

where $A_{m,ref}$ refers to the zero-strain mid-wall area reference. Subsequently, natural fiber strain at zero load $\varepsilon_{f,0}$ can be calculated from mid-wall area $A_{m,0}$

$$\varepsilon_{f,0} = 0.5 \cdot \log\left(\frac{A_{m,0}}{A_{m,ref}}\right) \quad \text{(S21)}$$

Fiber stress σ_f was calculated as a function of strain, using a phenomenological model as described in Supplemental Methods 1.1. Wall tension T_m can be related to fiber stress σ_f using the principle of conservation of energy [1]

$$T_m = \frac{\sigma_f \cdot V_w}{2 \cdot A_m} \quad \text{(S22)}$$

where V_w refers to the wall volume.

Systole was assumed to end when contraction reaches its maximum. The end-systolic fiber stress-strain relation was derived from a linear mid-wall tension area relation between the point of zero load and maximal contraction. The end-diastolic fiber stress-strain relation was defined by the passive fiber stress behavior as explained in Supplemental Methods 1.1.

The potential energy (PE) was defined as the area enclosed by the end-systolic stress-strain relation, diastolic limb of the stress-strain loop, end-diastolic stress-strain relation and the x-axis (Figure 2).

External work

The external work (EW) was defined as the area enclosed by the Cauchy myofiber stress-natural strain loop (Figure 2).

Myocardial oxygen demand

Total SSA (in Joule) was calculated as the sum of regional external work and potential energy, multiplied by the wall segment's volume. Division of SSA by the duration of the cardiac cycle reveals regional total mechanical power (TMP).

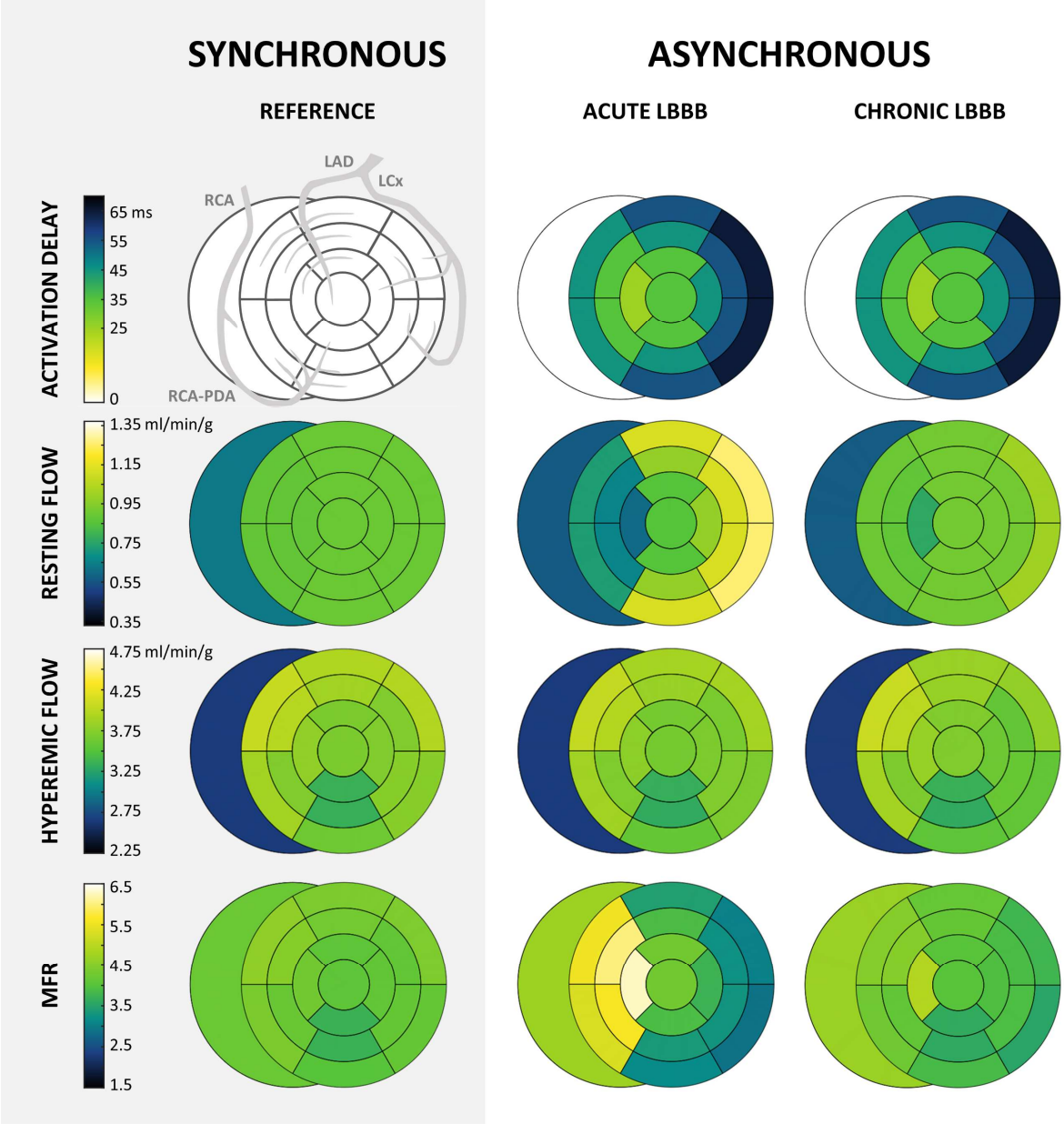
$$TMP = \frac{SSA}{t_{cycle}} \tag{S23}$$

Regional myocardial oxygen consumption was assumed to be related to TMP as follows

$$VO_{2,reg} = k_1 \cdot TMP + k_2 \tag{S24}$$

with $k_1 = 4.94\ mmol\ kJ^{-1}$ and $k_2 = 24.2\ mmol\ m^{-3}\ s^{-1}$, adopted from experimental studies in the paced canine heart [4].

2. Supplemental Figure



Supplemental Figure S1 Mapping of activation delay, resting and hyperemic flow, as well as myocardial flow reserve (MFR) under synchronous (REFERENCE) and asynchronous (ACUTE LBBB and CHRONIC LBBB) ventricular activation. Abbreviations: LAD: left anterior descending coronary artery, LCx: left circumflex coronary artery, PDA: posterior descending coronary artery, RCA: right coronary artery.

3. Supplemental Tables

3.1 Parameter values for the one-dimensional coronary network

The reference pressure (p_0) of coronary arterial and venous vessels were, similar to systemic arterial and venous vessels, equal to mean arterial pressure and mean right atrial pressure, respectively. The reference lumen area (A_0) of the vessels was approximated based on their respective flow distribution. The determination of wall area (A_w) was set to be dependent on wall stress and impact velocity (i.e. velocity of waves generated when jumping) [5]. The stiffness coefficient (k) was set to 11, similar to systemic proximal and distal vessels.

Supplemental Table S1 Arterial parameter values for the one-dimensional network.

	Vessel Name	Proximal Node	Distal Node	Length (cm)	Reference Area (cm^2)	Wall Area (cm^2)
Left main coronary arteries (LM)						
1	AoLM	Ao	LM	1.21	0.147	0.050
Left circumflex coronary arteries (LCx)						
2	LMLCx1	LM	LCx1	2.34	0.061	0.021
3	LCx1LCxbalAr	LCx1	LCxbalAr	1.00	0.012	0.004
4	LCx1LCx2	LCx1	LCx2	2.00	0.024	0.008
5	LCx2LCxmalAr	LCx2	LCxmalAr	1.00	0.012	0.004
6	LCx2LCxalAr	LCx2	LCxalAr	1.00	0.012	0.004
7	LCx1LCx3	LCx1	LCx3	2.10	0.024	0.008
8	LCx3LCxmilAr	LCx3	LCxmilAr	1.00	0.012	0.004
9	LCx3LCxbilAr	LCx3	LCxbilAr	1.00	0.012	0.004
Left anterior descending coronary arteries (LAD)						
10	LMLAD1	LM	LAD1	2.04	0.087	0.029
11	LAD1LADbaAr	LAD1	LADbaAr	1.00	0.012	0.004
12	LAD1LADbasAr	LAD1	LADbasAr	1.00	0.013	0.004
13	LAD1LAD2	LAD1	LAD2	1.74	0.062	0.021
14	LAD2LADmaAr	LAD2	LADmaAr	1.00	0.012	0.004
15	LAD2LADmasAr	LAD2	LADmasAr	1.00	0.013	0.004
16	LAD2LAD3	LAD2	LAD3	2.26	0.037	0.012
17	LAD3LADaaAr	LAD3	LADaaAr	1.00	0.012	0.004
18	LAD3LADasAr	LAD3	LADasAr	1.00	0.013	0.004
19	LAD3LADaAr	LAD3	LADaAr	1.00	0.012	0.004
Right coronary arteries (RCA)						
20	AoRCA1	Ao	RCA1	5.00	0.103	0.039
21	RCA1RCAAr	RCA1	RCAAr	1.00	0.041	0.018
22	RCA1RCA2	RCA1	RCA2	5.00	0.062	0.021
23	RCA2RCAbisAr	RCA2	RCAbisAr	1.00	0.013	0.004
24	RCA2RCA3	RCA2	RCA3	2.78	0.049	0.017
25	RCA3RCAmisAr	RCA3	RCAmisAr	1.00	0.013	0.004
26	RCA3RCAbiAr	RCA3	RCAbiAr	1.00	0.012	0.004
27	RCA3RCA4	RCA3	RCA4	2.47	0.024	0.008
28	RCA4RCAmiAr	RCA4	RCAmiAr	1.00	0.012	0.004
29	RCA4RCAaiAr	RCA4	RCAaiAr	1.00	0.012	0.004

Supplemental Table S2 Venous parameter values for the one-dimensional network.

	Vessel Name	Proximal Node	Distal Node	Length (cm)	Reference Area (cm^2)	Wall Area (cm^2)
Coronary sinus (CS)						
1	CsCs2	Cs	Cs2	1.21	0.147	0.010
Left circumflex coronary veins (LCx)						
2	Cs2VPL	Cs2	VPL	1.00	0.024	0.002
3	VPLLCxmilVe	VPL	LCxmilVe	1.00	0.012	0.001
4	VPLLCxbilVe	VPL	LCxbilVe	1.00	0.012	0.001
5	Cs2GCV	Cs2	GCV	2.10	0.123	0.009
6	GCVLCxbalVe	GCV	LCxbalVe	1.00	0.012	0.001
7	GCVGCV2	GCV	GCV2	2.00	0.024	0.002
8	GCV2LCxmalVe	GCV2	LCxmalVe	1.00	0.012	0.001
9	GCV2LCxalVe	GCV2	LCxalVe	1.00	0.012	0.001
10	GCVVAL	GCV	VAL	4.38	0.087	0.006
Left anterior descending coronary veins (LAD)						
11	VALLADbaVe	VAL	LADbaVe	1.00	0.012	0.001
12	VALLADbasVe	VAL	LADbasVe	1.00	0.013	0.001
13	VALVAL2	VAL	VAL2	1.74	0.062	0.004
14	VAL2LADmaVe	VAL2	LADmaVe	1.00	0.012	0.001
15	VAL2LADmasVe	VAL2	LADmasVe	1.00	0.013	0.001
16	VAL2VAL3	VAL2	VAL3	2.26	0.037	0.002
17	VAL3LADaaVe	VAL3	LADaaVe	1.00	0.012	0.001
18	VAL3LADasVe	VAL3	LADasVe	1.00	0.013	0.001
19	VAL3LADaVe	VAL3	LADaVe	1.00	0.012	0.001
Right coronary veins (RCA)						
20	CsMCV	Cs	MCV	1.21	0.103	0.008
21	MCVMCV2	MCV	MCV2	1.00	0.062	0.004
22	MCV2RCAbisVe	MCV2	RCAbisVe	1.00	0.013	0.001
23	MCV2MCV3	MCV2	MCV3	2.78	0.049	0.003
24	MCV3RCAmisVe	MCV3	RCAmisVe	1.00	0.013	0.001
25	MCV3RCAbiVe	MCV3	RCAbiVe	1.00	0.012	0.001
26	MCV3MCV4	MCV3	MCV4	2.47	0.024	0.002
27	MCV4RCAmiVe	MCV4	RCAmiVe	1.00	0.012	0.001
28	MCV4RCAaiVe	MCV4	RCAaiVe	1.00	0.012	0.001
29	MCVSCV	MCV	SCV	5.00	0.041	0.004
30	SCVRCAVe	SCV	RCAVe	1.00	0.041	0.004

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