

SUPPLEMENTAL MATERIAL

Table 1. Pre-operative baseline characteristics.

Variable	Patients (n=6)
Clinical data	
Age, years	59.6 ± 5.7
Age ≥ 70, n (%)	0 (0)
BMI	24.2 ± 1.0
Male, n (%)	6 (100)
Atrial fibrillation, n (%)	1 (16.7)
Hypertension, n (%)	3 (50.0)
Diabetes, n (%)	0 (0.0)
Coronary artery disease, n (%)	0 (0)
NYHA functional class III-IV	2 (33.3)
Echocardiographic data	
LVEF (%)	59.3 ± 4.6
LVEDD (mm)	61.8 ± 4.3
LVESD (mm)	43.3 ± 3.2
PISA radius (cm)	1.2 ± 0.2
EROA (cm ²)	0.5 ± 0.1
Regurgitant volume (ml)	69.3 ± 7.3
Regurgitant fraction (%)	59.5 ± 9.6
Vena contracta MR (mm)	7.2 ± 2.4
MR Grade 4+, n (%)	6 (100)
sPAP (mmHg)	44.7 ± 17.4

NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; PISA: proximal isovelocity surface area; EROA: effective regurgitant orifice area; MR, mitral regurgitation; sPAP: systolic pulmonary artery pressure.

Tables S2, S3: Inputs for computational modeling parameters.

Species information

module	ID	name	Yinit	Ymax	tau	type	gene name	notes
g-coupled	AngII	angiotensin II	0	1	1	1 protein	AGT	
g-coupled	AT1R	angiotensin II receptor type 1	0	1	0.1	protein	AGTR1;AGTR2	
g-coupled	AGT	angiotensinogen	0	1	10	protein	AGT	
g-coupled	ACE	angiotensin converting enzyme	0	1	0.1	protein	ACE; ACE2	
g-coupled	NOX	NAD(P)H oxidase	0	1	0.1	protein	NOX4; NOX5	
g-coupled	ROS	reactive oxygen species	0	1	0.1	protein		
g-coupled	ET1	endothelin 1	0	1	1	protein	EDN1	
g-coupled	ETAR	endothelin 1 receptor A	0	1	0.1	protein	EDNRA	
g-coupled	DAG	diacyl-glycerol	0	1	0.1	small		
g-coupled	PKC	protein kinase C	0	1	0.1	protein	PRKCA; PRKCE;	
pressure/stretch	TRPC	transient receptor potential canonical	0	1	0.1	protein	TRPC6;TRPC3	
g-coupled	NE	norepinephrine	0	1	1	small		
g-coupled	BAR	beta adrenergic receptor 1 or 2	0	1	0.1	protein	ADRB1; ADRB2	
g-coupled	Forskolin		0	1	1	small		
g-coupled	AC	adenylate cyclase	0	1	0.1	protein	ADCY6	
g-coupled	cAMP	cyclic adenosine monophosphate	0	1	0.1	small		
g-coupled	PKA	protein kinase A	0	1	0.1	protein	PRKACA	
g-coupled	CREB	cAMP response-element binding protein	0	1	0.1	protein	CREB1; CREB3	
g-coupled	CBP	CREB - binding protein	0	1	0.1	protein	CREBBP	
growth factor	TGFB	transforming growth factor beta 1	0	1	1	protein	TGFB1	
growth factor	TGFB1R	TGFB receptor	0	1	0.1	protein	TGFBRI; TGFBRI2	
growth factor	smad3	small mothers against decapentaplegic 2 and 3	0	1	0.1	protein	SMAD2; SMAD3	
growth factor	smad7		0	1	10	protein	SMAD7	
growth factor	latentTGFB	TGFB1 with latent protein complex	0	1	10	protein	TGFB1	
growth factor	BAMBI	BMP and activin bound inhibitor	0	1	0.1	protein	BAMBI	
growth factor	PDGF	platelet derived growth factor	0	1	1	protein	PDGFA; PDGFB; PDGFD	
growth factor	PDGFR	platelet derived growth factor receptor	0	1	0.1	protein	PDGFRA; PDGFRB	
g-coupled	NP	natriuretic peptide	0	1	1	protein	NPPA; NPPB	
g-coupled	NPRA	natriuretic peptide receptor	0	1	0.1	protein	NPR1; NPR2; NPR3	
g-coupled	cGMP	cyclic guanosine monophosphate	0	1	0.1	small		
g-coupled	PKG	protein kinase G	0	1	0.1	protein	PRKG1	
pressure/stretch	tension	stretch	0	1	1	process		
pressure/stretch	B1int	beta 1 integrin	0	1	0.1	protein	ITGB1	
pressure/stretch	Rho	a Rho-dependent GTPase	0	1	0.1	protein	RHOA	
pressure/stretch	ROCK	rho associated protein kinase	0	1	0.1	protein	ROCK1	
pressure/stretch	Ca	calcium	0	1	0.1	small		
pressure/stretch	calcineurin	calcineurin	0	1	0.1	protein	PPP3CA; PPP3CB	
pressure/stretch	NFAT	nuclear factor of activated T-cells	0	1	0.1	protein	NFATC1	
cytokine	IL6	interleukin-6	0	1	1	protein	IL6	
cytokine	gp130	IL-6 receptor complexed to gp130 for signal trans	0	1	0.1	protein	IL6ST; IL6R	
cytokine	STAT	signal transducers and activators of transcription 1	0	1	0.1	protein	STAT1; STAT3	
cytokine	IL1	interleukin-1 alpha and beta	0	1	1	protein	IL1B; IL1A	
cytokine	IL1RI	IL1 receptor type I	0	1	0.1	protein	IL1RI	
cytokine	TNFa	tissue necrosis factor alpha	0	1	1	protein	TNF	
cytokine	TNFaR	TNF alpha receptor	0	1	0.1	protein	TNFRSF1A;TNFRSF1B	
cytokine	NFKB	nuclear factor kappa-light-chain-enhancer of activ	0	1	0.1	protein	NFKB1	
cytokine	PI3K	phosphoinositide 3-kinase	0	1	0.1	protein	PIK3CA	
cytokine	Akt	protein kinase B	0	1	0.1	protein	AKT1; AKT2; AKT3	
MAPK	p38	a MAP kinase	0	1	0.1	protein	MAPK14	
MAPK	TRAF	tnf receptor associated factor either 2/6	0	1	0.1	protein	TRAF6	
MAPK	ASK1	apoptosis signal related kinase 1	0	1	0.1	protein	MAP3K5	
MAPK	MKK3	mitogen activated protein kinase kinase	0	1	0.1	protein	MAP2K3	
MAPK	PP1	protein phosphatase 1	0	1	0.1	protein	PPP1CA; PPP1CB; PPP1CC	
MAPK	JNK	a MAP kinase	0	1	0.1	protein	MAPK8	
MAPK	abl	abl tyrosine kinase	0	1	0.1	protein	ABL1; ABL2	
MAPK	Rac1	a Rho-dependent GTPase	0	1	0.1	protein	RAC1	
MAPK	MEKK1	a MAP3K associated with p38 and JNK	0	1	0.1	protein	MAP3K1	
MAPK	MKK4	a MAP2K associated with p38 and JNK	0	1	0.1	protein	MAP2K4	
MAPK	ERK	a MAP kinase	0	1	0.1	protein	MAPK1; MAPK3	
MAPK	Ras	representing the family of GTPases	0	1	0.1	protein	KRAS	
MAPK	Raf	family of raf protein serine/threonine kinases	0	1	0.1	protein	RAF1	
MAPK	MEK1	a MAP2K mainly specific to ERK	0	1	0.1	protein	MAP2K1	
adhesion	FAK	focal adhesion kinase	0	1	0.1	protein	PTK2	
g-coupled	epac	exchange protein activated by cAMP 1	0	1	0.1	protein	RAPGEF3	
adhesion	Factin	polymerized actin	0	1	1		ACTG1	
adhesion	FA	stabilization of focal adhesions	0	1	1	complex		
growth	cmyc	myc transcription factor	0	1	0.1	protein	MYC	
growth	CTGF	connective tissue growth factor	0	1	0.1	protein	CTGF	
growth	proliferation	proliferation	0	1	10	event		
adhesion	SRF	serum response factor	0	1	0.1	protein	SRF	
ECM	EDAFN	extra domain A of fibronectin	0	1	10	protein	FN1	
adhesion	aSMA	alpha-smooth muscle actin	0	1	10	protein	ACTA2	
MAPK	AP1	activator protein 1	0	1	0.1	protein	JUN; FOS	
ECM	TIMP1	tissue inhibitor of metalloproteinase 1	0	1	10	protein	TIMP1	
ECM	TIMP2	tissue inhibitor of metalloproteinase 2	0	1	10	protein	TIMP2	
ECM	PAI1	plasminogen activator inhibitor 1	0	1	10	protein	SERPINE1	

ECM	proMMP14	inactive MMP14	0	1	10	protein	MMP14
ECM	proMMP1	inactive MMP1	0	1	10	protein	MMP1
ECM	proMMP2	inactive MMP2	0	1	10	protein	MMP2
ECM	proMMP9	inactive MMP9	0	1	10	protein	MMP9
ECM	fibronectin	fibronectin	0	1	10	protein	FN1
ECM	periostin	periostin	0	1	10	protein	POSTN
ECM	proCI	procollagen I	0	1	10	protein	COL1A1
ECM	proCIII	procollagen III	0	1	10	protein	COL3A1
pressure/stretch	B3int	beta 3 integrin	0	1	0.1	protein	ITGB3
adhesion	Src	proto-oncogene tyrosine-protein kinase Src	0	1	0.1	protein	SRC1
MAPK	Grb2	growth factor receptor-bound protein 2	0	1	0.1	protein	GRB2
adhesion	p130Cas	breast cancer anti-estrogen resistance protein 1	0	1	0.1	protein	BCAR1
pressure/stretch	YAP	yes-associated protein 1	0	1	0.1	protein	YAP1
adhesion	MRTF	myocardin-related transcription factor A	0	1	0.1	protein	MRTFA; MKL1
adhesion	Gactin	monomeric actin	0	1	1	protein	ACTG1
ECM	TNC	tenascin-c	0	1	10	protein	TNC
growth	mTORC1	mammalian target of rapamycin complex 1	0	1	0.1	complex	
growth	mTORC2	mammalian target of rapamycin complex 2	0	1	0.1	complex	
growth	p70S6K	p70-S6 kinase 1	0	1	0.1	protein	RPS6KB1
growth	EBP1	eukaryotic translation initiation factor 4E-binding 1	0	1	0.1	protein	EIF4EBP1
pressure/stretch	syndecan4	syndecan 4	0	1	0.1	protein	SDC4
ECM	proMMP3	inactive MMP3	0	1	1	protein	MMP3
ECM	proMMP8	inactive MMP8	0	1	1	protein	MMP8
ECM	proMMP12	inactive MMP12	0	1	1	protein	MMP12
ECM	thrombospondin4	thrombospondin 4	0	1	10	protein	THBS4
ECM	osteopontin	osteopontin	0	1	10	protein	SPP1
adhesion	contractility	intracellular tension	0	1	10	event	
pressure/stretch	RhoGEF	a Rho guanine nucleotide exchange factor	0	1	0.1	protein	
pressure/stretch	RhoGDI	a Rho GDP-dissociation inhibitor	0	1	0.1	protein	
adhesion	tal1	tal1 1	0	1	0.1	protein	TLN1
adhesion	vinculin	vinculin	0	1	0.1	protein	VCL
adhesion	paxillin	paxillin	0	1	0.1	protein	PXN
adhesion	MLC	myosin regulatory light chain	0	1	0.1	protein	MYL2
Cilia	PKD1	polycystin-1	0	1	1	protein	
Cilia	PKD2	polycystin-2	0	1	1	protein	
pressure/stretch	TRPV4	TRPV channel	0	1	1	protein	
g-coupled	IP3R	inositol triphosphate receptor	0	1	1	protein	
Cilia	DZIP1	DAZ Interacting Zinc Finger Protein 1	0	1	1	protein	
Cilia	CBY1	Protein chibby homolog 1	0	1	1	protein	
cytokine	Beatenin	Beta-catenin	0	1	1	protein	
g-coupled	SMO	Smoothed	0	1	1	protein	
cytokine	DHH	Desert Hedgehog	0	1	1	protein	
cytokine	TIAM1	T-lymphoma invasion and metastasis-inducing pro	0	1	1	protein	
cytokine	WNT	WNT	0	1	1	protein	
cytokine	Pak1	p21 (Rac1) Activated Kinase 1	0	1	1	protein	
cytokine	Flna	filamin-a	0	1	1	protein	
cytokine	Hic5	Transforming Growth Factor Beta 1 Induced Tra	0	1	1	protein	
cytokine	Ptch1	Patched 1	0	1	1	protein	
cytokine	Gli2	GLI Family Zinc Finger 2	0	1	1	protein	
cytokine	Runx2	HH pathway transcription factor	0	1	1	protein	
ECM	ADAMTS4	A Disintegrin and Metalloproteinase with Thromb	0	1	10	protein	
ECM	ADAMTS5	A Disintegrin and Metalloproteinase with Thrombc	0	1	10	protein	
ECM	ADAMTS9	A Disintegrin and Metalloproteinase with Thrombc	0	1	10	protein	
ECM	proMMP13	inactive MMP13	0	1	10	protein	
cytokine	Fz	Frazzled	0	1	1	protein	
cytokine	Dvl	Disheveled	0	1	1	protein	
cytokine	Groucho	Groucho	0	1	1	protein	
cytokine	TCF	TCF/LEF1 transcription factors	0	1	1	protein	
ECM	versican	Versican	0	1	1	protein	
protein	GSK3B	GSK3B	0	1	1	protein	

Reaction Information

module	ID	Rule	Weight	n	EC50	source	notes	PMID	Secondary Reference	Tertiary Reference	AND references
input	i1	=> AngII	0.1	1.3	0.55	neonatal rat cardiac fibroblasts	increased via RAS in hypertension and heart failure	10362677			
input	i2	=> TGFβ	0.1	1.3	0.55		increased in response to injury	20538689			
input	i3	=> tension	0.1	1.3	0.55		increased with integrin stimulation	9547793			
input	i4	=> IL6	0.1	1.3	0.55		increased in hypertension	19234091			
input	i5	=> IL1	0.1	1.3	0.55			19631653			
input	i6	=> TNFα	0.1	1.3	0.55			10591022			
input	i7	=> NE	0.1	1.3	0.55		most likely NE signaling	3948363			
input	i8	=> PDGF	0.1	1.3	0.55		increased post-MI	20538689			
input	i9	=> ET1	0.1	1.3	0.55		increased from stretch of vascular endothelial cells	12695528			
input	i10	=> NP	0.1	1.3	0.55		increased in pressure	17991884			
input	i11	=> Forskolin	0	1.3	0.55						
fback	r1	proMMP9 & latentTGFβ => TGFβ	0.25	1.3	0.55	in vitro	release of latent protein	10652271	MC3T3-E1	12226090	
fback	r2	proMMP2 & latentTGFβ => TGFβ	0.25	1.3	0.55	in vitro	release of latent protein	10652271	MC3T3-E1	12226090	
fback	r3	ACE & AGT => AngII	0.25	1.3	0.55	neonatal cardiac fibroblasts	enzymatic modification	10790312	in vitro	13295487	
fback	r4	CREB & CBP => IL6	0.25	1.3	0.55	neonatal rat cardiac fibroblasts	txn	11597988	mouse cardiac fibroblasts	16466739	10405202
fback	r5	NFKB => IL6	0.25	1.3	0.55	neonatal rat cardiac fibroblasts	txn	11597988		16466739	
fback	r6	API => IL6	0.25	1.3	0.55	neonatal cardiac fibroblasts	txn	11597988	sv40 murine cells	16466739	
fback	r7	API => ET1	0.25	1.3	0.55	neonatal rat cardiac fibroblasts	txn	12695528	bovine aortic endothelial cells	1918021	
middle	r8	AngII => AT1R	1	1.3	0.55	neonatal cardiac fibroblasts	receptor binding	8348686	adult rat cardiac fibroblasts	16024575	
middle	r9	AT1R => NOX	1	1.3	0.55	adult rat cardiac fibroblast	-	15106793	neonatal rat cardiac fibroblasts	11597988	
middle	r10	NOX => ROS	1	1.3	0.55	adult rat cardiac fibroblast	enzymatic production	15106793	adult rat cardiac fibroblasts	16531806	
middle	r11	IL6 => gp130	1	1.3	0.55	neonatal rat cardiac fibroblasts	receptor binding	19234091	COS7 cells	1602143	
middle	r12	ROS => ERK	1	1.3	0.55	neonatal rat cardiac fibroblasts	activation	11597988	neonatal rat cardiac fibroblasts	14642698	12695528
middle	r13	ROS => p38	1	1.3	0.55	neonatal rat cardiac fibroblasts	activation	11597988	neonatal rat cardiac fibroblasts	24882408	12695528
middle	r14	ROS => JNK	1	1.3	0.55	neonatal rat cardiac fibroblasts	activation	11597988	neonatal rat cardiac fibroblasts	12695528	
middle	r15	IL1R1 => NFKB	1	1.3	0.55	neonatal rat cardiac fibroblasts	release of blocking and increased abundance	11597988	human foreskin fibroblasts	1906501	
middle	r16	gp130 => STAT	1	1.3	0.55	neonatal mouse fibroblasts	activation (via JAK)	19234091	murine proB cell line	9874564	
middle	r17	TNFα => PI3K	1	1.3	0.55	human cardiac fibroblasts	activation	17560598	human cardiac fibroblast	17612514	
middle	r18	!AT1R & !JNK & p38 => AGT	1	1.3	0.55	neonatal rat cardiac fibroblasts	txn	18926830	neonatal rat cardiac fibroblasts	21131638	11192370
middle	r19	TGFβ1R & !PKG & !smad7 => smad3	1	1.3	0.55	adult rat cardiac fibroblast	activation	17513491	COS7 cells	9335507, 9215638	17991884, 17038494
output	r20	smad3 & CBP & ERK => CTGF	1	1.3	0.55	neonatal rat cardiac fibroblasts	txn	18586263	mouse cardiac fibroblasts	22749815	11013125, 12368229, 16959941
output	r21	STAT => proMMP2	1	1.3	0.55	neonatal rat cardiac fibroblasts	txn	15550851	human lung cell lines	24573038	
output	r22	STAT => proMMP9	1	1.3	0.55	mouse cardiac fibroblasts	txn	19234091	human genome database	18258475	
output	r23	smad3 & CBP => periostin	1	1.3	0.55	adult rat cardiac fibroblasts	txn	21367774	gingival fibroblasts	24004653	
output	r24	CREB & CBP => periostin	1	1.3	0.55	adult rat cardiac fibroblasts	txn	21367774	murine dermal fibroblast	24577408	16959941
middle	r25	ERK => NFKB	1	1.3	0.55	human cardiac fibroblast	activation	17921324	periodontal ligament fibroblast	21757573	
middle	r26	p38 => NFKB	1	1.3	0.55	human cardiac fibroblast	activation	17921324	NIH-3T3 (via CBP)	11259436	
output	r27	NFKB & API & !smad3 => proMMP1	1	1.3	0.55	human cardiac fibroblast	txn	17921324	human dermal fibroblasts	11502752	12525489
middle	r28	ETAR => ROS	1	1.3	0.55	neonatal rat cardiac fibroblasts	activation	12695528	neonatal rat cardiac fibroblasts	16391241	
middle	r29	ERK => API	1	1.3	0.55	neonatal rat cardiac fibroblasts	activation	12695528	human lung fibroblast	10862759	
output	r30	API => proMMP2	1	1.3	0.55	human cardiac fibroblasts	txn	17921324	neonatal rat cardiac fibroblasts	12371906	
output	r31	API & NFKB => proMMP9	1	1.3	0.55	human cardiac fibroblasts	txn	17560598	human foreskin fibroblasts	9755853	
output	r32	API => TIMP1	1	1.3	0.55	human cardiac fibroblasts	txn	17921324	human foreskin fibroblasts	9182725	
output	r33	API => TIMP2	1	1.3	0.55	human cardiac fibroblast	txn	17921324	3T3 and rat fibroblast	8112602	
middle	r34	PKC & tension => B1int	1	1.3	0.55	adult rat cardiac fibroblasts	activation	15949469	mouse embryonic fibroblasts	12110574	21131638
middle	r35	cAMP => PKA	1	1.3	0.55	adult rat cardiac fibroblasts	activation	11054474	cardiac fibroblast	21977288	
output	r36	smad3 & CBP => fibronectin	1	1.3	0.55	human lung fibroblast	txn	16707625	human cardiac fibroblast	11013125	
middle	r37	!smad3 => CBP	1	1.3	0.55	adult rat cardiac fibroblasts	depletion of txn factor binding partner	16959941	human dermal fibroblasts	10918613	
middle	r38	!CREB => CBP	1	1.3	0.55	adult rat cardiac fibroblasts	depletion of txn factor binding partner	16959941	3T3 cells	8028671	
middle	r39	tension => B1int	1	1.3	0.55	neonatal rat cardiac fibroblasts	activation	21131638	NIH-3T3	15760908	
output	r40	NFAT => EDAFN	1	1.3	0.55	neonatal mice cardiac fibroblast	txn activation	23178899	rat cardiac fibroblasts	23142541	
middle	r41	TGFβ1R => ACE	1	1.3	0.55	rat cardiac fibroblasts	increased txn	11967821	human cardiac myofibroblasts	18223028	
middle	r42	TGFβ & !BAMBI => TGFβ1R	1	1.3	0.55	mice cardiac fibroblast	binding to receptor	22960625	mouse cardiac fibroblasts	24078695	
middle	r43	API => proliferation	1	1.3	0.55	adult rat cardiac fibroblasts	via activation of Kca3.1 channels	23500546	adult rat cardiac fibroblasts	17483238	
middle	r44	PKA => CREB	1	1.3	0.55	rat cardiac fibroblasts	activation	11054474	mouse embryonic fibroblasts	11909979	
middle	r45	CREB => proliferation	1	1.3	0.55	rat cardiac fibroblasts	activation	11054474	rat cardiac fibroblasts	17483238	
middle	r46	NE => BAR	1	1.3	0.55	rat cardiac fibroblasts	receptor binding	11054474	rat pineal gland	7700241	
middle	r47	ET1 => ETAR	1	1.3	0.55	neonatal rat cardiac fibroblasts	receptor binding	12695528	adult rat cardiac fibroblasts	8313418	
middle	r48	CTGF => proliferation	1	1.3	0.55	human cardiac fibroblast	activation	11013125	rat cardiac fibroblasts	17483238	
middle	r49	IL1 => IL1R1	1	1.3	0.55	mouse cell line	receptor binding	8327496	neonatal rat cardiac fibroblasts	7769098	
middle	r50	PKC => proliferation	1	1.3	0.55	adult rat cardiac fibroblasts	activation	10756114	adult rat cardiac fibroblasts	17483238	
output	r51	smad3 & CBP & !epac => proCI	1	1.3	0.55	adult rat cardiac fibroblasts	txn	17513491	adult rat cardiac fibroblasts	17513491	11279127, 18434542, 23845590
output	r52	smad3 & CBP & !epac => proCHI	1	1.3	0.55	adult rat cardiac fibroblasts	txn	17513491	adult rat cardiac fibroblasts	17513491	11279127, 18434542, 23845590
output	r53	API => proMMP14	1	1.3	0.55	mouse cardiac fibroblasts	correlated increase with cFOS	22287584	mouse embryonic fibroblasts	17348021	
middle	r54	PDGF => PDGFR	1	1.3	0.55	adult rat cardiac fibroblasts	receptor binding	11230972	rat cardiac fibroblasts	24427322	
middle	r55	BAR => AC	1	1.3	0.55	adult rat cardiac fibroblasts	activation	12711600	rat cardiac fibroblasts	17934720	
middle	r56	BAR & AT1R => AC	1	1.3	0.55	adult rat cardiac fibroblasts	activation with potentiation	12711600	rat dermal fibroblasts	1330500	
middle	r57	AC => cAMP	1	1.3	0.55	adult rat cardiac fibroblasts	activation	12711600	human pulmonary fibroblast	15075208	
middle	r58	FAK => MEKK1	1	1.3	0.55	mouse embryonic fibroblasts	activation	17409352	mouse embryonic fibroblasts	12458213	21131638
output	r59	API => latentTGFβ	1	1.3	0.55	mouse lung fibroblasts	txn activation	20141610	adult rat cardiac fibroblasts	21367774	22429882, 19374881
middle	r60	cAMP => epac	1	1.3	0.55	adult rat cardiac fibroblasts	activation	18434542	NIH-3T3	9853756	
middle	r61	Rho => ROCK	1	1.3	0.55	rat embryonic fibroblasts	activation	16043513	rat cardiac fibroblasts	17456553	
middle	r62	TNFα => TNFαR	1	1.3	0.55	human cardiac fibroblast	receptor binding	17560598	mouse cardiac fibroblasts	23337087	
middle	r63	NP => NPRA	1	1.3	0.55	human cardiac fibroblast	receptor binding	16986166	COS7 cells	11595171	
middle	r64	NPRA => cGMP	1	1.3	0.55	adult rat cardiac fibroblast	activation	17991884	human cardiac fibroblast	16986166	
middle	r65	cGMP => PKG	1	1.3	0.55	adult rat cardiac fibroblast	activation	17991884	mouse cardiac fibroblasts	21282499	
middle	r66	Ras => Raf	1	1.3	0.55	neonatal rat cardiac fibroblast	possibly via recruitment and Src phosphorylation	9486662	NIH-3T3	8668210	
middle	r67	Raf & !ERK => MEK1	1	1.3	0.55	adult rat cardiac fibroblast	activation	12388314	NIH-3T3	8668210	21943356, 24489118
middle	r68	MEK1 & !PP1 => ERK	1	1.3	0.55	adult rat cardiac fibroblast	activation	12388314	NIH-3T3	12167697	11259586, 15972258,
middle	r69	p38 => PP1	1	1.3	0.55	3T3 cells, adult and neonatal human dermal fibroblast	via activation	11259586	human endothelial cells	15972258	25659900
middle	r70	MKK3 => p38	1	1.3	0.55	3T3 cells, adult and neonatal human dermal fibroblast	activation	11259586	human synovioctes	15778394	
middle	r71	TGFβ1R => TRAF	1	1.3	0.55	adult mouse cardiac fibroblast	activation	22749815	mouse embryonic fibroblasts	18922473	
middle	r72	Rac1 => MEKK1	1	1.3	0.55	NIH-3T3, HeLa	activation	7600582	ovarian cancer cells	9674706	
middle	r73	MEKK1 => MKK4	1	1.3	0.55	NIH-3T3, HeLa	activation	7600582	cos1, HeLa	12401521	
middle	r74	MKK4 & !NFKB => JNK	1	1.3	0.55	NIH-3T3, HeLa	activation	7600582	NIH-3T3	16076903	11713530, 11466617

middle	r75	PDGFR => abl	1	1.3	0.55	3T3	activation	16076903	mouse embryonic fibroblasts	10500097	
middle	r76	abl => Rac1	1	1.3	0.55	3T3	activation	16076903	mouse embryonic fibroblasts	15039778	
middle	r77	JNK => cmyc	1	1.3	0.55	3T3	activation	16076903	NIH-3T3	14523011	
middle	r78	cmyc => proliferation	1	1.3	0.55	3T3	activation	16076903	NIH-3T3	15195135	
middle	r79	TNFA => TRAF	1	1.3	0.55	293 cells	activation	9774977	human cardiac fibroblast	17560598	10523862
middle	r80	TRAF => ASK1	1	1.3	0.55	293 cells	activation - most likely binding allows the receptor to eventua	9774977	293, cos7, mouse embryonic fibroblas	10523862	
middle	r81	ASK1 => MKK3	1	1.3	0.55	COS7 cells	activation	8974401	human foreskin fibroblasts	10912795	
middle	r82	ASK1 => MKK4	1	1.3	0.55	COS7 cells	activation	8974401	human embryonic lung fibroblasts	19494316	9774977
middle	r83	IL1R1 => ASK1	1	1.3	0.55	fibroblast-like synoviocytes	assumed activation	15778394	human foreskin fibroblasts	10912795	
middle	r84	smad3 => PAI1	1	1.3	0.55	adult mouse cardiac fibroblast	transcription	17991884	Hep2g cells	9606191	11279127
output	r85	NFKB => proMMP14	1	1.3	0.55	human dermal fibroblast	transcription	11112697	human breast cancer cell line	20855151	
middle	r86	Ras => p38	1	1.3	0.55	adult rat cardiac fibroblast	unknown	21367774	human foreskin fibroblasts	14593117	
middle	r87	TGFB1R => PI3K	1	1.3	0.55	adult rat cardiac fibroblast	activation	21498085	NIH-3T3	16288034	
middle	r88	PDGFR => PI3K	1	1.3	0.55	3T3	activation	21943356	adult rat cardiac fibroblasts	11230972	
middle	r89	FAK => PI3K	1	1.3	0.55	human lung fibroblast	activation	15166238	human bone marrow mesenchymal ste	25900259	
middle	r90	TGFB1R => NOX	1	1.3	0.55	human cardiac fibroblast	activation	16179589	human dermal fibroblasts	26096997	25858818
middle	r91	Akt => NFKB	1	1.3	0.55	human cardiac fibroblast	activation by removal of IKK	18064631	human dermal fibroblasts, rat synovio	10485711	
output	r92	NFKB => fibronectin	1	1.3	0.55	human cardiac fibroblast	transcription	18064631	rat osteoblasts	17252537	23141425
middle	r93	JNK => AP1	1	1.3	0.55	human periodontal ligament fibroblast	activation	21757573	neonatal rat cardiac fibroblasts	12695528	
middle	r94	IL1R1 & TGFB => BAMBI	1	1.3	0.55	mice cardiac fibroblast	increased transcription (unsure of transcription factor)	24078695	adult rat cardiac fibroblasts	23734837	
middle	r95	Forskolin => AC	1	1.3	0.55	adult rat cardiac fibroblast	drug action	12711600	human lung fibroblast	15075208	
middle	r96	STAT => smad7	1	1.3	0.55	U4A cell line	STAT necessary for smad expression	10067896	human lung fibroblast	11927620	22751114
output	r97	SRF => proCI	1	1.3	0.55	10t1/2 cells, cardiac fibroblasts	MRTF directly activates the expression of COL1	20558820	NIH-3T3, mouse embryonic fibroblast	24732378	
middle	r98	Rho & !Rac1 => p38	1	1.3	0.55	neonatal rat cardiac fibroblast		21131638	murine mesangial cells	25007875	
middle	r99	MKK4 & !Rho => JNK	1	1.3	0.55	neonatal rat cardiac fibroblast		21131638	NIH-3T3	7600582	
output	r100	SRF => proCIII	1	1.3	0.55	mouse cardiac fibroblasts		20558820	NIH-3T3, mouse embryonic fibroblast	24732378	
output	r101	SRF & smad3 & CBP => aSMA	0	1.3	0.55	human cardiac fibroblast		16179589	mouse embryonic fibroblasts	20558820	24732378
middle	r102	calcineurin => NFAT	1	1.3	0.55	mouse cardiac fibroblasts	activation/nuclear translocation	22403241	neonatal mouse cardiac fibroblast	23178899	
middle	r103	AT1R => Ras	1	1.3	0.55	neonatal cardiac fibroblasts		9486662	adult rat cardiac fibroblasts	21367774	
output	r104	smad3 & CBP => aSMA	1	1.3	0.55	human cardiac fibroblast	txn activation	16179589	rat gingival fibroblasts	26738448	
output	r105	SRF => aSMA	1	1.3	0.55	rat cardiac fibroblasts	transcription	17456553	mouse embryonic fibroblasts	15855636	
middle	r106	ETAR => DAG	1	1.3	0.55	rat embryonic fibroblasts	production	1809396	mouse embryonic fibroblasts	10676846	
middle	r107	AT1R => DAG	1	1.3	0.55	CHO cells	production	7653525	rat cardiac fibroblasts	17982962	
middle	r108	DAG => TRPC	1	1.3	0.55	human cardiac fibroblast	activation	17533154	adult rat cardiac fibroblasts	22992321	25521631
middle	r109	TRPC & tension => Ca	1	1.3	0.55	human cardiac fibroblast	channel opening	23827314	adult rat cardiac fibroblasts	22992321	
middle	r110	Ca => calcineurin	1	1.3	0.55	adult rat cardiac fibroblast	activation	26191219	rat dermal fibroblasts	23022034	
middle	r111	TGFB1R => Rho	1	1.3	0.55	human gingival fibroblasts		16953819	human colonic fibroblasts	24280883	29700112
middle	r112	B3int => Src	1	1.3	0.55	human lung fibroblasts	dephosphorylation: Y530, autophosphorylation: Y419	18353785	CHO cells	14593208	
middle	r113	B1int => FAK	1	1.3	0.55	mouse embryonic fibroblasts, COS7	autophosphorylation: Y397	7529876	mouse embryonic fibroblasts	10413676	23589296
middle	r114	FAK & Src => Grb2	1	1.3	0.55	mouse embryonic fibroblasts	activation via Src	7997267	mouse embryonic fibroblasts	9032297	8816475
middle	r115	Grb2 => Ras	1	1.3	0.55	rat cardiac fibroblasts	activation via SOS	9486662	mouse embryonic fibroblasts, HEK293	8479541	7997267
middle	r116	FAK & Src => RhoGEF	1	1.3	0.55	mouse embryonic fibroblasts	activation	18195107	mouse embryonic fibroblasts	18303050	19339545
middle	r117	!Src => RhoGDI	1	1.3	0.55	mouse embryonic fibroblasts, HeLa	phosphorylation: decreases binding Rho binding affinity	16943322	293T	19321744	
middle	r118	FAK & Src => p130Cas	1	1.3	0.55	mouse embryonic fibroblasts	activation via Src	9032297	CHO cells	9425168	16581250
middle	r119	PDGFR => Src	1	1.3	0.55	mouse embryonic fibroblasts	activation	8356071	mouse embryonic fibroblasts	10222144	9739761
middle	r120	tension & Src => p130Cas	1	1.3	0.55	mouse embryonic fibroblasts	activation	8670206	mouse embryonic fibroblasts	22499769	17129785
middle	r121	p130Cas & abl => Rac1	1	1.3	0.55	HEK293	activation	10385525	293T	18793427	17533370
middle	r122	Factin => YAP	1	1.3	0.55	mouse embryonic fibroblasts	nuclear translocation	23644383	mouse embryonic fibroblasts	26757814	24648494
middle	r123	PKA => RhoGDI	1	1.3	0.55	rat cardiac fibroblasts	phosphorylation	23012358	COS7 cells	18768928	
middle	r124	RhoGEF & !RhoGDI => Rho	1	1.3	0.55	mouse embryonic fibroblasts	activation	18303050	mouse embryonic fibroblasts	22649559	24467208
output	r125	YAP => CTGF	1	1.3	0.55	mouse embryonic fibroblasts	txn via TEAD	18579750	MCF10A	19324877	29563341
middle	r126	syndecan4 => PKC	1	1.3	0.55	rat embryonic fibroblasts	activation	22504297	rat embryonic fibroblasts	12571249	16787950
middle	r127	!PKC => RhoGDI	1	1.3	0.55	rat embryonic cardiomyocytes	phosphorylation	15316932	human umbilical vein endothelial cells	11309397	
middle	r128	!Gactin & NFAT => MRTF	0	1.3	0.55	mouse cardiac fibroblasts	translocation	23178899	mouse dermal fibroblasts	23022034	
middle	r129	!Gactin & Hic5 => MRTF	1	1.3	0.55	mouse embryonic fibroblasts	translocation	18025109	mouse embryonic fibroblasts	12475943	12475943
middle	r130	ROCK & Gactin => Factin	1	1.3	0.55	rat cardiac fibroblasts	polymerization	17456553	mouse embryonic fibroblasts	12732141	26721596
middle	r131	!Factin => Gactin	1	1.3	0.55	mouse embryonic fibroblasts	polymerization	12475943	mouse embryonic fibroblasts	12732141	
middle	r132	MRTF => SRF	1	1.3	0.55	human lung fibroblasts		22461426	mouse embryonic fibroblasts	12732141	26721596
fback	r133	!TNC & tension => syndecan4	1	1.3	0.55	mouse dermal fibroblasts	dephosphorylation	15483051	T98G	11731446	19339214
middle	r134	Akt => mTORC1	1	1.3	0.55	HEK293	activation via TSC1/2, PRAS40 inhibition	12172553	mouse embryonic fibroblasts	16027121	19117990
middle	r135	mTORC1 => p70S6K	1	1.3	0.55	mouse embryonic fibroblasts	activation	21602892	mouse embryonic fibroblasts	16027121	19117990
middle	r136	!mTORC1 => EBP1	1	1.3	0.55	mouse embryonic fibroblasts	phosphorylation	23940704	HEK293	9465032	29518028
middle	r137	!EBP1 & p70S6K => proliferation	1	1.3	0.55	rat cardiac fibroblasts	mRNA translation	16270752	human lung fibroblasts	21784851	15522879
middle	r138	Akt => smad3	1	1.3	0.55	mouse cardiac fibroblasts	activation via GSK3B inhibition	24899689	mouse embryonic fibroblasts	19458083	17604717
output	r139	NFKB => TNC	1	1.3	0.55	human cardiac fibroblasts	txn	23454256	chick embryonic fibroblasts	15363633	20107185
output	r140	MRTF => TNC	1	1.3	0.55	mouse embryonic fibroblasts	txn	21705668	chick embryonic fibroblasts	15363633	
middle	r141	!p70S6K => mTORC2	1	1.3	0.55	mouse embryonic fibroblasts	phosphorylation via Rictor	19995915	HEK293	19720745	
middle	r142	mTORC2 & PI3K => Akt	1	1.3	0.55	mouse embryonic fibroblasts	activation	23311350	mouse embryonic fibroblasts	18566587	15718470
middle	r143	mTORC2 & DAG => PKC	1	1.3	0.55	HEK293	activation	15268862	mouse embryonic fibroblasts	18566587	17604717
output	r144	YAP => PAI1	1	1.3	0.55	human lung fibroblasts	txn	25502501	mouse embryonic fibroblasts	27881410	
middle	r145	smad3 => thrombospondin4	1	1.3	0.55	human dermal fibroblasts	txn	30132849	mouse lung endothelial cells	28481870	
fback	r146	!thrombospondin4 & tension => B3int	1	1.3	0.55	mouse cardiac fibroblasts	receptor binding	25987545	human ligament fibroblasts	19647831	20884877
output	r147	NFKB & AP1 & !smad3 => proMMP8	1	1.3	0.55	mouse cardiac fibroblasts	txn	30686120	human mesenchymal stem cells	24738865	19805288
output	r148	NFKB & AP1 & !smad3 => proMMP3	1	1.3	0.55	mouse cardiac fibroblasts	txn	30686120	human cardiac fibroblasts	20619343	17706606
output	r149	AP1 => osteopontin	1	1.3	0.55	rat cardiac fibroblasts	txn	14755545	rat lung fibroblasts	16211580	
fback	r150	osteopontin => B3int	1	1.3	0.55	rat cardiac fibroblasts	receptor binding	8941637	human lung fibroblasts	16128620	
output	r151	CREB => proMMP12	1	1.3	0.55	human dermal fibroblasts	txn	23671273			
middle	r152	AP1 & !YAP => smad7	1	1.3	0.55	human dermal fibroblasts	txn: YAP/TAZ knock-down required for smad7 expression	29695252	mouse embryonic fibroblasts	11402315	10843994
middle	r153	FAK & Src & MLC => paxillin	1	1.3	0.55	human foreskin fibroblasts	activation	20308429	mouse embryonic fibroblasts, PAEC	17164291	
middle	r154	vinculin & !paxillin => FA	1	1.3	0.55	human foreskin fibroblasts	stabilization: paxillin increases FA turnover for increased mig	18056416	mouse embryonic fibroblasts, PAEC	17164291	
middle	r155	B1int => talin	1	1.3	0.55	mouse embryonic fibroblasts	activation	18056416	mouse embryonic fibroblasts	27065098	
middle	r156	B3int => talin	1	1.3	0.55	mouse embryonic fibroblasts	activation	27065098	mouse fibroblast-like cells	14581461	
middle	r157	talin & contractility => vinculin	1	1.3	0.55	mouse embryonic fibroblasts	activation	18056416	mouse embryonic fibroblasts	27065098	
middle	r158	Factin & MLC => contractility	1	1.3	0.55	mouse embryonic fibroblasts	binding via vinculin tail region	18056416	mouse embryonic fibroblasts	23716647	
fback	r159	contractility & FA => tension	1	1.3	0.55	human foreskin fibroblasts	force generation via molecular clutch theory	28592635	human foreskin fibroblasts	2859772	26121555
middle	r160	ROCK => MLC	1	1.3	0.55	mouse embryonic fibroblasts	activation via MLCK activation, MBS inhibition	10953004	rat embryonic fibroblasts	16043513	

middle	r161	Cilia => PKD1	1	1.3	0.55	mouse embryonic kidney cells	direct co-localization in WT at basal body and ciliary tubulin	12514735	mouse kidney epithelium	12239239		
middle	r162	Cilia => PKD2	1	1.3	0.55	mouse kidney cells	direct co-localization in WT at basal body and ciliary tubulin	12062067	mouse embryonic kidney cells	12514735		
middle	r163	Cilia & tension => PKD1	1	1.3	0.55	VSMCs	PKD1 needed for response to inc pressure	19879844	chondrocytes (cyclic)	22223751		
middle	r164	PKD1 => PKD2	1	1.3	0.55	mouse embryonic kidney cells	direct co-localization in WT at basal body and ciliary tubulin	12514735	COS cells, kidney epithelium, aortic ept	19879844		
middle	r165	PKD2 => TRPV4	1	1.3	0.55	mouse endothelial cells	tension = shear stress	19265036	kidney epithelial cells	12514735	18695040	keratinocytes
middle	r166	PKD2 & tension => NOX	1	1.3	0.55	mouse endothelial cells	tension = shear stress	19265036	primary osteocytes	24268313		
middle	r167	TRPV4 & tension => Ca	1	1.3	0.55	pulmonary adventitial fibroblasts		31693393	pulmonary fibroblasts	29126921		
middle	r168	PKD1 & B1int => FAK	1	1.3	0.55	medullary collecting duct cells	co-ip and activation when plated on fibronectin	16790429	MDCk cells	25947155		
middle	r169	PKD2 => IP3R	1	1.3	0.55	Xenopus cells		16223735	human kidney epithelium	22456092		
middle	r170	PKD2 & IP3R => Ca	1	1.3	0.55	Xenopus cells		16223735	human kidney epithelium	22456092		
middle	r171	Cilia => DZIP1	1	1.3	0.55	valve interstitial cell	co-immunoprecipitation	31118289	mouse embryonic fibroblasts	23955340		
middle	r172	DZIP1 => CBV1	1	1.3	0.55	valve interstitial cell	co-immunoprecipitation	Guo et al. 2020	confirmed with yeast 2-hybrid screen			
middle	r173	ICB1 => Bcatenin	1	1.3	0.55	valve interstitial cell	cby1 knockdown leads to increased nuclear B-catenin	Guo et al. 2020	mouse respiratory epithelium	19364920	12712206	18573912
input	i12	=> DHH	0.1	1.3	0.55		increased during cardiac development	32151560				
middle	r174	Cilia & DHH & IPtch1 => SMO	1	1.3	0.55	valve interstitial cell		28556366	valve interstitial cell	32151560	17641202	22474285
middle	r175	SMO => TIAM1	1	1.3	0.55	valve interstitial cell		32151560	mouse embryonic fibroblasts, pyramida	20654717		
middle	r176	TIAM1 => Rac1	1	1.3	0.55	valve interstitial cell		32151560	human dermal fibroblasts	20802514		
middle	r177	Cilia & PDGF => PDGFR	0.25	1.3	0.55	MEFs		20110689	NIH3T3 cells	16243034		
input	i13	=> WNT	0.1	1.3	0.55		increased during cardiac development and matrix production	22819513				
middle	r178	Cilia & TGFB => TGFB1R	0.25	1.3	0.55	mouse embryonic fibroblasts	dec cilia => dec receptor function	23746451	mesenchymal stem cells	27748449		
fback	r179	periostin => B1int	1	1.3	0.55	valve interstitial cell		30742951	valve interstitial cell	24469446		
middle	r180	Akt => Pak1	1	1.3	0.55	valve interstitial cell		30742951	valve interstitial cell	24469446		
fback	r181	periostin => B3int	1	1.3	0.55	valve interstitial cell		24469446	valve interstitial cell	30742951		
middle	r182	Flna & tension => B1int	1	1.3	0.55	HEK293	FLNA binds to cytoplasmic tail of B1int	18177638	T cells	9722563		
middle	r183	Rac1 => Pak1	1	1.3	0.55	Human 293T cells	rac1 needed for activation of Pak1 at membrane	11804587	Fibroblasts	11134074		
middle	r184	Pak1 => ERK	1	1.3	0.55	valve interstitial cell		24469446	mouse medullary collecting duct cells	23781022		
middle	r185	Pak1 => Flna	1	1.3	0.55	3T3 fibroblasts	co-immunoprecipitation	32389644	MCF-7 cells	12198493		
middle	r186	FAK => Hic5	1	1.3	0.55	293T cells		9858471	rat fibroblast (WFB)	9422762		
middle	r187	SMO => Gli2	1	1.3	0.55	Valve interstitial cell		32151560	vascular adventitial fibroblasts	29088375		
middle	r188	Gli2 => Runx2	1	1.3	0.55	osteoblast		17442891	mouse fetal cardiac cells	18813803		
middle	r189	Runx2 => ADAMTS5	1	1.3	0.55	chondrocytes		21094261	synovial fibroblasts	27449198		
middle	r190	Runx2 => ADAMTS4	1	1.3	0.55	Chondrocytes		21094261	synovial fibroblasts	27449198		
middle	r191	Runx2 => ADAMTS9	1	1.3	0.55	chondrocytes		21094261	synovial fibroblasts	27449198		
middle	r192	Runx2 => proMMP13	1	1.3	0.55	chondrocytes		21094261	chondrocytes	16868966		
middle	r193	!tension => Cilia	1	1.3	0.55	tenocytes	cyclic stress lead => cilia length	20957738	chondrocytes (cyclic)	24457103	human endothelial cells	15024030
middle	r194	Cilia & Gactin => Factin	0.25	1.3	0.55	chondrocytes	cilia loss is associated with decreased F-actin organization	26493329	chondrocytes	17359961		
middle	r195	WNT & Cilia => Fz	1	1.3	0.55	mouse cardiac fibroblasts		30040870	conserved across species and cell types	19147006		
middle	r196	Fz => Dvl	1	1.3	0.55	mouse cardiac fibroblasts		30040870	conserved across species and cell types	19147006		
middle	r197	!Dvl => GSK3B	1	1.3	0.55	mouse cardiac fibroblasts		30040870	conserved across species and cell types	19147006		
middle	r198	!GSK3B => Bcatenin	1	1.3	0.55	mouse cardiac fibroblasts		30040870	conserved across species and cell types	19147006		
middle	r199	!Bcatenin => Groucho	1	1.3	0.55	mouse cardiac fibroblasts		30040870	conserved across species and cell types	19147006		
middle	r200	!Groucho => TCF	1	1.3	0.55	mouse cardiac fibroblasts		30040870	conserved across species and cell types	19147006		
middle	r201	!Cilia => Bcatenin	1	1.3	0.55	MEFs		18084282	MEFs	21602792		
middle	r202	Rac1 & smad3 => NOX	1	1.3	0.55	NIH-3T3	Rac activates Nox	8809022	VSMC	16514078		
middle	r203	NOX => MLC	1	1.3	0.55	mouse myofibroblasts		24403605	lung VSMC	18621909		
middle	r204	Bcatenin & MRTF => SRF	1	1.3	0.55	LLC-PK1 cells	potentially through a de-repressor action	21965288	MCF-7 cells	29632640		
middle	r205	TCF => fibronectin	1	1.3	0.55	mouse lung fibroblasts		15617677	embryonic stem cells	18983966		
middle	r206	TCF => versican	1	1.3	0.55	VSMCs		15668231	human melanoma cells	19269971		
middle	r207	aSMA & MLC => contractility	1	1.3	0.55	mouse myofibroblasts		19800625	rat lung fibroblasts	18086923		
fback	r208	tension & latentTGFB => TGFB	0.25	1.3	0.55	rat lung fibroblasts	contraction & stretch can release active TGFB from LBP	18086923	HCC cells	28025149		

Supplemental Figure Legends:

Figure S1: Regional fibrosis in MVP patients. (A) Patient age and leaflet involvement are listed. (B) Masson's histochemical stain at low magnification showing entire biopsy region and prominent fibrosis (blue) in peri-papillary region compared to within-person tissues from either apex or septum. (C) Same patient biopsies immunostained for collagen I (black). Scale bars = 1mm.

Figure S2: Evidence of sarcomeric loss in myocytes. Biopsy from MVr patient shows well elaborated myocytes (purple) with definable sarcomeric organization and no detectable fibrosis within the apex region. Within the same patient, prominent fibrosis and sarcomeric disorganization/loss (arrows) are prominent within fibrotic (collagen-yellow) zones in peri-papillary regions. Scale bars are 50 μ m.

Figure S3: Regional fibrosis correlates with increased macrophages in MVP. Septal (top) and peri-papillary biopsies were obtained from the same patient during MVr and IHC was performed for collagen (yellow), CD163 (purple) and nuclei (Hoechst-blue). Uniquely within the peri-papillary region, prominent fibrosis and CD163⁺ macrophages are observed.

Figure S4: Full network of all input nodes used in computational modeling. Interconnections between all nodes from >300 publications of cardiac fibroblast molecular and mechanobiology were interpolated.

Figure S5: Heat map of all significant differentially expressed genes. 232 statistically significant differentially expressed genes between stretched and static human cardiac fibroblasts are represented.

Supplemental Video Legends:

Video S1: 2D TEE echocardiography showing prominent posterior leaflet prolapse

Video S2: 3D TEE echocardiography showing prominent posterior leaflet prolapse

Video S3 and S4: Cardiac MRI with late gadolinium enhancement showing evidence of peri-papillary and inferobasal myocardial fibrosis

Video S5: Mitral valve repair showing prominent anterior leaflet prolapse and gross inspection of intramyocardial papillary fibrosis (white dense material) and absence of fibrosis in the apex tissue. Yellow color = fat

A

Patient	Age	Leaflet Involvement
MI-LVF-001	62	P2
MI-LVF-002	53	P1, P2, P3
MI-LVF-003	55	P2
MI-LVF-004	69	P2
MI-LVF-005	61	A2, P2
MI-LVF-006	58	A3, P3

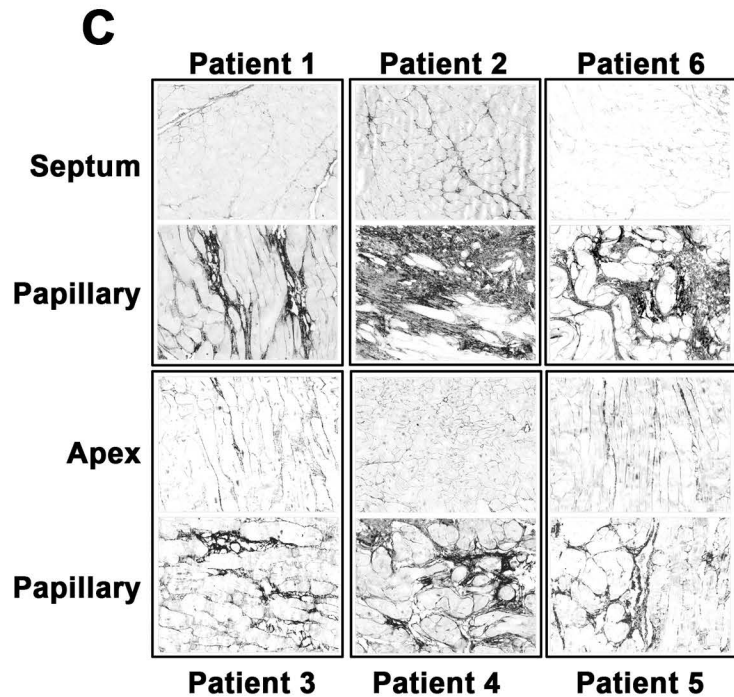
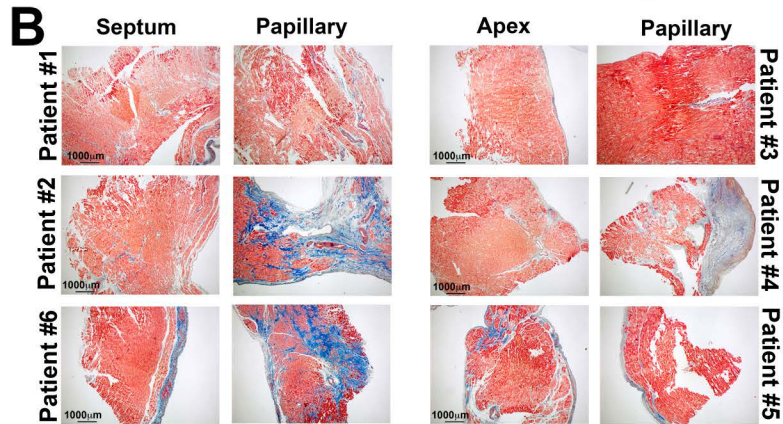
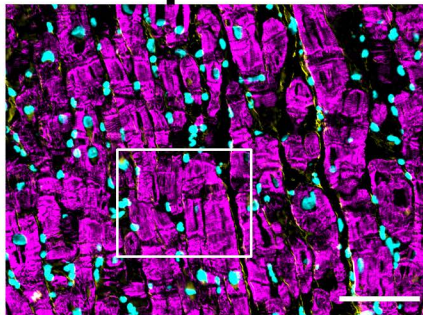
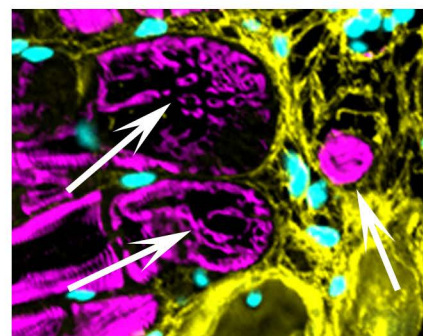
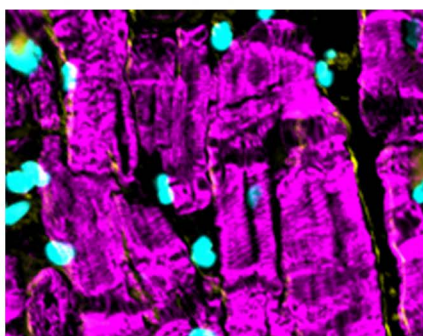
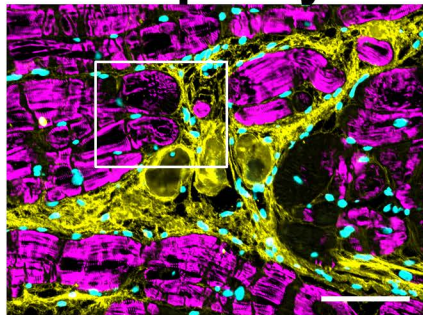


Figure S1

Apex



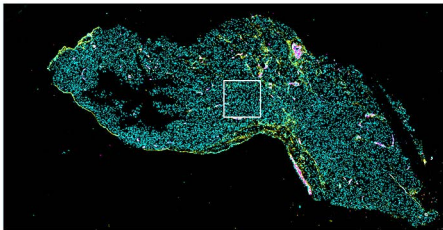
Papillary



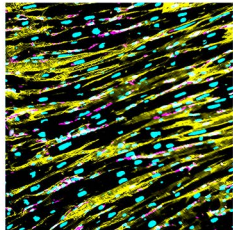
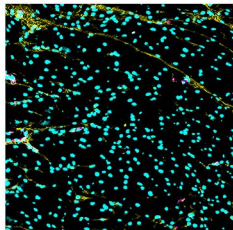
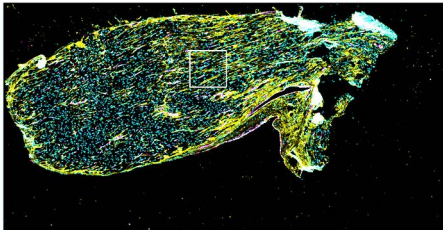
Collagen/Myocytes/Nuclei

Figure S2

Septum



Papillary



Collagen/CD163/Hoechst

Figure S3

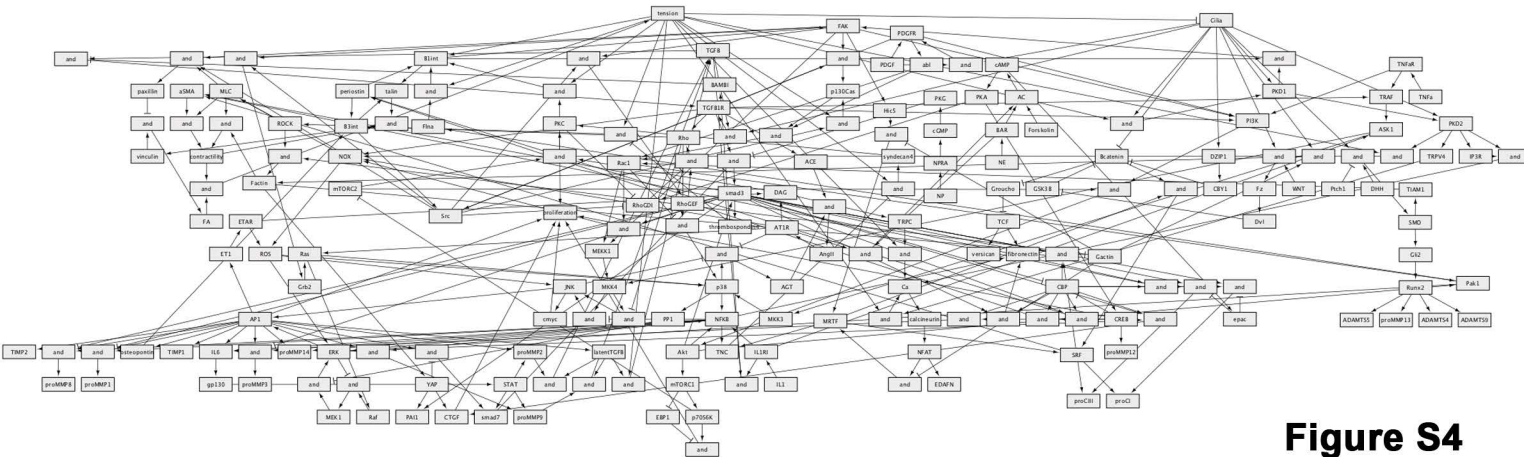


Figure S4

