

# Analysis of Patient-specific Surgical Ventricular Restoration - Importance of an Ellipsoidal Left Ventricular Geometry for Diastolic and Systolic Function

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## 44 **Summary**

45 Surgical ventricular restoration (SVR) is a procedure designed to treat heart failure by surgically  
46 excluding infarcted tissues from the dilated failing left ventricle. To elucidate and predict the effects of  
47 geometrical changes from SVR on cardiac function, we created patient-specific mathematical (finite  
48 element) left ventricular models before and after surgery using untagged magnetic resonance images. Our  
49 results predict that the post-surgical improvement in systolic function was compromised by a decrease in  
50 diastolic distensibility in patients. These two conflicting effects typically manifested as a more depressed  
51 Starling relationship (stroke volume vs. end-diastolic pressure) after surgery. By simulating a restoration  
52 of the left ventricle back to its measured baseline sphericity, we show that both diastolic and systolic  
53 function improved. This result confirms that the increase in left ventricular sphericity commonly observed  
54 after SVR (endoventricular circular patch plasty) has a negative impact and contributes partly to the  
55 depressed Starling relationship. On the other hand, peak myofiber stress was reduced substantially (by  
56 50%) after SVR and the resultant left ventricular myofiber stress distribution became more uniform. This  
57 significant reduction in myofiber stress after SVR may help reduce adverse remodeling of the left  
58 ventricle. These results are consistent with the speculation proposed in the STICH trial (20) for the neutral  
59 outcome, that “the lack of benefit seen with surgical ventricular reconstruction is that benefits anticipated  
60 from surgical reduction of left ventricular volume (reduced wall stress and improvement in systolic  
61 function) are counter-balanced by a reduction in diastolic distensibility.”

62

63 **Keywords:** Myocardial infarction, Surgical ventricular restoration, Finite element modeling, Coronary  
64 artery bypass grafting.

65

66 Word Count: 243

## 67 **Introduction**

68 Surgical ventricular restoration (SVR) is a procedure designed to treat heart failure by surgically  
69 excluding infarcted tissues from the dilated failing left ventricle (LV). The aim of this treatment is to  
70 neutralize the negative physiologic effects of dysfunctional regions in the left ventricular wall. The  
71 “Surgical Treatment for Ischemic Heart Failure” (STICH) trial was conducted to assess the effectiveness  
72 of SVR (35). One of the two components of the trial was to determine whether adding SVR to Coronary  
73 Artery Bypass Grafting (CABG) would decrease the rate of death or hospitalization for cardiac  
74 causes more than CABG alone. The clinical findings led the authors to conclude that adding SVR to  
75 CABG reduces the LV volume compared to CABG alone, but this reduction is not associated with a  
76 greater improvement in symptoms, exercise tolerance or a reduction in the rate of death or  
77 hospitalization for cardiac causes. One speculation for these findings was that the benefits anticipated  
78 from the surgical reduction of LV volume were counterbalanced by a reduction in diastolic  
79 distensibility (21).

80 Although the STICH trial concluded that SVR, when performed with CABG, adds no benefits to  
81 the patient, this conclusion remains controversial (7, 8, 26). Clinical studies have shown that SVR did  
82 benefit patients who had myocardial infarction (3, 4, 8, 19, 24, 28) and both the European Society of  
83 Cardiology and European Association for Cardio-Thoracic Surgery recommend SVR if LV volume is  
84 measured, scar is identified and surgery is performed in centers with a high level of surgical expertise  
85 (37). Conversely, clinical studies have also shown that stroke volume (SV) decreased after SVR (13, 22,  
86 34, 39), and the decrease in size of the LV after SVR can be accompanied by an increase in LV sphericity  
87 (12, 23, 39). This post-surgical increase in LV sphericity was believed to impair diastolic function (27).  
88 On the other hand, the supposedly lower ventricular wall stress (based on Laplace’s law) resulting from a  
89 reduction in LV size after SVR should in principle benefit patients by reducing myocardial oxygen  
90 demand (30). These conflicting effects of SVR contribute, in part, to the gap in our understanding as to  
91 why patients who underwent SVR did not always receive the benefits from the supposedly lower wall

92 stress. Bridging this gap requires accurate quantification of the local myofiber stress, which at present,  
93 can be determined only through patient-specific mathematical modeling (38).

94 Patient-specific mathematical modeling of the effects of SVR is largely lacking and is, at best,  
95 overly simplified. Many mathematical analyses of SVR have been conducted based on animal LV  
96 models. For example, a mathematical model of the sheep LV by Dang et al. (10) was used to study the  
97 effects of SVR alone (without CABG) on diastolic distensibility, end-systolic elastance, the Starling  
98 relationship (SV versus end-diastolic pressure) and regional myofiber stress distribution. Their  
99 results suggest that when compared to the remote region, SVR reduces myofiber stress in the akinetic  
100 infarct and infarct borderzone. They also found that the Starling relationship was depressed after SVR.  
101 However, this result is based on a sheep LV and did not address the increase in sphericity of the post-  
102 surgical LV commonly found in patients. On the other hand, a recent analysis of the patient-specific  
103 effects of SVR found it reduced the LV bulk wall stress and improved the LV systolic function (40). That  
104 analysis was based on a local balance of forces, however, and cannot account for myofiber orientation or  
105 predict myofiber stress distribution within the LV (38).

106 To elucidate the functional effects resulting from the geometrical change found in the LV after  
107 SVR, we performed the first mathematical analysis on the effects of SVR using patient-specific finite  
108 element (FE) LV models. These models were created using untagged magnetic resonance (MR) images  
109 from the same set of patient data described in Zhong et al. (39).

## 110 **Material and Methods**

### 111 *Acquisition of magnetic resonance images*

112 The method used for magnetic resonance imaging (MRI) is detailed in Zhong et al. (40). All procedures  
113 in patients were approved by our institutional review board and patient consents were obtained. The MR  
114 images were de-identified. Images were obtained one to two weeks before surgery and one to two weeks  
115 after surgery with a 1.5-T MRI scanner (Siemens Somatom, Erlangen, Germany). These images were

116 segmented interactively by outlining the LV endocardial and epicardial borders (excluding papillary  
117 muscles and trabeculation) using CMRtools. Then, the set of LV contour points derived from the  
118 segmentation process was triangulated using Rapidform<sup>®</sup> (INUS Technology, Inc) to reconstruct the  
119 three-dimensional (3D) LV epicardial and endocardial surfaces. End-diastolic (ED) and end-systolic (ES)  
120 cardiac phases were determined by visualizing the mitral valve and the aortic valve closure.

### 121 ***Finite element modeling***

122 We used the FE method to analyze the effects of surgery (CABG + SVR) in 12 patients (randomly  
123 selected from a cohort of 40 patients). In each patient, the SVR procedure was performed using the  
124 endoventricular circular patch plasty technique. Three of these 12 patients had concomitant mitral  
125 regurgitation and underwent mitral valve repair surgery by means of restrictive mitral annuloplasty. A  
126 multivariable general linear model analysis was performed on this patient cohort and did not detect any  
127 differences between patients who received mitral valve repair surgery (MVR) and patients who did not  
128 receive MVR (39). Finite element models of the LV were created by projecting a mesh between the 3D  
129 endocardial and the 3D epicardial surface reconstructed from the acquired MR images (33) at early  
130 diastole (Truegrid, XYZ Scientific Applications, Inc., Livermore, CA). The mesh in each LV model  
131 consisted of between 2000 to 4000 trilinear 8-noded brick elements.

132 In the pre-surgery models, two distinct material regions were defined: the transmural infarct  
133 region and the remote region. The infarct region was defined as the region without any relative wall  
134 motion; i.e., akinesia. The remote-infarct boundary was identified by overlapping the ED and the ES  
135 endocardial surface. Then, this boundary was projected transmurally onto the epicardial surface. In the  
136 post-surgery models, the entire LV was assumed to be composed of a single material as there were no  
137 significant overlapping regions. Residual stress was not included in the post-surgery LV models because  
138 the effects were found to be negligible in a previous study (16). Rigid body motion of the LV was  
139 suppressed by constraining the base from moving in the longitudinal direction and by constraining the  
140 epicardial-basal edge from moving in all directions.

141 Myofiber angle distribution was assumed to vary transmurally from epicardium to endocardium  
142 via a linear transition from  $-60^\circ$  to  $+60^\circ$  relative to the circumferential direction in all models (16, 29).  
143 Also, we have recently obtained unpublished *ex-vivo* diffusion tensor magnetic resonance imaging  
144 (DTMRI) fiber angle measurements from 5 explanted human hearts with ischemic heart failure. The  
145 myofiber angle was found to vary transmurally from  $-42.4^\circ$  (epicardium) to  $35.7^\circ$  (endocardium) on  
146 average. To test whether the conclusions of our analysis would be impacted if these new fiber angle data  
147 were used, we repeated the analysis on one LV model using these new fiber data.

148 Because pressure was not measured in the LV, the end-systolic pressure (ESP) was assumed to  
149 match the measured systolic blood pressure (SBP) of individual patients. The average SBP of the  
150 patients was 121 mmHg pre-surgery and 117 mmHg post-surgery. End-diastolic pressure (EDP) was  
151 assumed to be 12 mmHg pre-surgery and post-surgery. The pressure was applied to the LV endocardial  
152 surface. To assess the sensitivity of the pressure-volume and Starling relationship to EDP and ESP, we  
153 repeated the analysis with EDP at 4 and 20 mmHg and ESP at 90% and 110% of the SBP. The sensitivity  
154 of the end-systolic myofiber stress to ESP was also assessed for each case. We note that the estimation of  
155  $ESP = 0.9 \times$  systolic blood pressure, as was used in many studies; e.g. in (6), falls within the range of ESP  
156 used in our sensitivity analysis. Although the sensitivity analysis did not account for inter-individual  
157 differences in the LV pressure (especially in EDP), it did confirm that the overall conclusions of this  
158 study are not sensitive to the LV pressure assumptions.

159 Passive and active constitutive laws previously described by Guccione et al. (17, 18) were used in  
160 this study (see Appendix A.1). The constitutive laws were implemented with a user-defined material  
161 subroutine in LS-DYNA (Livermore Software Technology Corporation, Livermore, CA). Passive  
162 stiffness of myocardial tissue was characterized by the material parameter  $C$  in the constitutive law.  
163 To obtain  $C$  in each of the model, we adjusted the  $C$ -values so that the predicted LV cavity volume  
164 of the FE model matched the measured end-diastolic volume (EDV). In the pre-surgery models,  $C$   
165 at infarct ( $C_I$ ) was set to be ten times stiffer than that in the remote region ( $C_R$ ) (36). Myocardial

166 tissue contractility in the active constitutive law was characterized by the material parameter  $T_{\max}$ , which  
167 is the strength of contraction at the longest sarcomere length in the tissue. In the post-surgery FE models,  
168  $T_{\max}$  was adjusted so that the predicted LV cavity volume matched the measured end-systolic volume  
169 (ESV). In the pre-surgery FE models,  $T_{\max}$  at the infarct ( $T_{\max_I}$ ) and at the remote region ( $T_{\max_R}$ ) were  
170 optimized so that: (i) the radial strain was nominally zero at the infarct because changes in wall thickness  
171 are minimal in akinesia, and (ii) the predicted LV cavity volume subjected to ESP was within  $\pm 1\%$  of the  
172 measured ESV. The optimization was implemented using LS-OPT (Livermore Software Technology  
173 Corporation, Livermore, CA). The approach of determining active material parameters in the pre-surgery  
174 models was adopted from Dang et al. (11), who have used FE models extrapolated from 2D  
175 echocardiography to examine akinetic infarcts. Although our models did not physically include any post-  
176 surgical implants (e.g. rigid rings, patches), the mechanical effects of these implants were, nevertheless,  
177 reflected in the material parameters  $C$  and  $T_{\max}$  as they were calculated based on the MRI-measured LV  
178 volumes and LV pressures that are within a physiological range.

179 Two post-surgery FE models were used to perform a study on the effects of LV sphericity, which  
180 was quantified by the short-to-long-axis ratio or sphericity index (SI). The long axis dimension was  
181 defined to be the apex to base distance and the short axis dimension was defined to be the maximum  
182 epicardial diameter measured at the mid-LV; i.e., half way between apex and base. A large value of SI  
183 indicates a more spherical LV, whereas a small value of SI indicates a more ellipsoidal LV. To simulate a  
184 change in SI, a downward force was applied at the apical region to elongate the LV and a negative  
185 pressure was concurrently applied at the mid-basal endocardial wall to ensure that the LV cavity volume  
186 remained constant. Then, the resultant LV geometry was used as the initial “stress-free” configuration to  
187 which the same fiber angle distribution was assigned. Because the myocardial material is incompressible,  
188 the LV wall mass remained constant after the LV shape was modified. The downward force was not  
189 present in subsequent analyses performed on the resultant LV. This force was used purely for modifying

190 the geometry of the LV. The corresponding post-surgery material parameters  $C$  and  $T_{\max}$  were used in the  
 191 elongated LV models.

## 192 ***Pressure–volume and Starling relationships***

193 Global LV performance was quantified using the pressure-volume relationship at ED and ES, as well as  
 194 by the Starling relationship. To obtain the end-diastolic pressure-volume relationship (EDPVR), the FE  
 195 models were used to predict the LV EDV at different EDP ranging between 0 to 25 mm Hg. Then, the  
 196 resulting pressure-volume relationship was fitted using an exponential function

$$EDP = A(e^{K_{ED}(EDV - V_{o,ED})} - 1). \quad (1)$$

197 In Eq. (1),  $A$ ,  $V_{o,ED}$  and  $K_{ED}$  are the fitting parameters. The parameter  $V_{o,ED}$  is the LV volume at zero  
 198 pressure, whereas the parameters  $K_{ED}$  and  $A$  affect the LV compliance during filling. Diastolic function  
 199 was quantified using the linear slope of EDPVR at 12mmHg ( $E_{ED}$ ). An improvement in diastolic  
 200 function was characterized by a decrease in  $E_{ED}$ .

201 The end-systolic pressure-volume relationship (ESPVR) was obtained from the FE models by  
 202 simulating the LV at different ESP, ranging from 0 to 140 mmHg. The computed LVESVs were fitted  
 203 to the corresponding applied ESPs using a linear function (2, 31) as given in the next equation:

$$ESP = E_{ES}(ESV - V_{o,ES}). \quad (2)$$

204 An improvement in systolic function is characterized by an increase in the end-systolic elastance  
 205  $E_{ES}$  i.e., the gradient of the linear fit, as well as by a decrease in the volume intersection  $V_{o,ES}$  of the  
 206 ESPVR. The simultaneous improvement of the diastolic and systolic function translates to an  
 207 improvement in SV and the Starling relationship.



208 To calculate the Starling relationship, we followed the approach used in Dang et al. (10). The  
209 arterial elastance was calculated (for each case) from the measured SV, the measured EDV, the fitted  
210  $E_{ES}$  and the volume–intersect  $V_{o,ES}$  of the ESPVR using Eq. (3) in Dang et al. (10). Then, the Starling  
211 relationship (SV-EDP) was obtained using that same equation by substituting for these values as well as  
212 for the computed EDPVR. We note that SV was not compensated in the 3 patients who had concomitant  
213 mitral regurgitation and underwent mitral valve repair surgery. In the study on the effects of sphericity,  
214 the arterial elastance was kept constant in each of the two groups. We have chosen here to use SV to  
215 quantify the LV performance instead of ejection fraction (EF) because EF is not an independent measure  
216 of LV performance after SVR (i.e., it is also sensitive to the decrease in EDV after surgery).

217

## 218 **Results**

219 Unless otherwise indicated, all results are reported as mean  $\pm$  standard deviation. Individual results from  
220 each patient are shown in the supplemental materials.

### 221 ***Reconstructed left ventricular geometries and hemodynamics measurements***

222 Figure 1a shows a representation of the pre-surgery and post-surgery FE LV model from 12 patients. The  
223 remote region is illustrated by the lighter region, and, in the pre–surgery models, the darker region  
224 illustrates the infarct. On average, measured EDV decreased by  $92.7 \pm 31.0$  ml (from  $269.6 \pm 63.5$  ml to  
225  $176.9 \pm 58.0$  ml) and measured ESV decreased by  $78.7 \pm 30.1$  ml (from  $210.4 \pm 62.5$  ml to  $131.7 \pm 63.2$   
226 ml) after surgery. The measured heart rate of these patients increased by  $6.8 \pm 9.5$  beats/min after surgery  
227 (from  $73.0 \pm 8.4$  beats/min to  $79.8 \pm 8.4$  beats/min) and the corresponding cardiac output decreased by  $0.6$   
228  $\pm 1.5$  L/min (from  $4.3 \pm 1.2$  L/min and  $3.6 \pm 1.5$  L/min) after surgery. Measured systemic vascular  
229 resistance index increased by  $620 \pm 1890$  dyn.s.cm<sup>-5</sup>.m<sup>-2</sup> (from  $2670 \pm 660$  dyn.s.cm<sup>-5</sup>.m<sup>-2</sup> to  $3290 \pm 1820$   
230 dyn.s.cm<sup>-5</sup>.m<sup>-2</sup>) after surgery. We also found that the LV became invariably more spherical after surgery  
231 as illustrated in Fig. 1b. On average, SI increased by 30%, from  $0.72 \pm 0.07$  to  $0.98 \pm 0.11$  after surgery.

## 232 ***Predicted global LV performance***

233 Figure 2 shows a representation of the effects of surgery on the ESPVR and EDPVR found in a typical  
234 patient. The bounds of the pressure-volume relationship from the sensitivity analysis are also displayed in  
235 the figure. We found that ESPVR consistently shifted to the left and became steeper after surgery. On  
236 average, the decrease in volume-intersect  $V_{o,ES}$  after surgery was  $64.1 \pm 26.2$  ml (from  $159.2 \pm 51.0$  ml to  
237  $95.1 \pm 51.3$  ml), and the end-systolic elastance  $E_{ES}$  increased by more than 1.5 times (from  $2.40 \pm 0.81$   
238 mmHg/ml to  $3.93 \pm 2.20$  mmHg/ml). Global systolic function therefore improved after surgery. This  
239 result was also insensitive to the choice of ESP. For the range of ESP at 90% - 110% of the SBP, the  
240 average values of  $V_{o,ES}$  and  $E_{ES}$  before surgery fell within 158.4 – 160.0 ml and 2.22 - 2.57 mmHg/ml,  
241 respectively. After surgery, the average values of  $V_{o,ES}$  and  $E_{ES}$  for this range of ESP fell within 94.7 –  
242 95.7 ml and 3.55 - 4.25 mmHg/ml, respectively.

243 Although global systolic function improved, global diastolic function to worsen after surgery and  
244 the LV became less compliant during filling. Specifically,  $E_{ED}$  increased from  $0.48 \pm 0.15$  mmHg/ml to  
245  $0.82 \pm 0.46$  mmHg/ml after surgery. For the range of EDP of 4 - 20 mmHg, the average value of  $E_{ED}$   
246 before surgery fell within 0.45 - 0.52 mmHg/ml, respectively. After surgery, the average values of  $E_{ED}$   
247 for this range of EDP fell within 0.78 - 0.92 mmHg/ml, respectively. Therefore, the decrease in global  
248 diastolic function predicted by our mathematical models was also insensitive to the choice of EDP.

249 These counteracting effects found in the ESPVR and EDPVR typically translated to a more  
250 depressed Starling relationship. The predicted Starling relationship remained unchanged in three patients  
251 (Fig. 3a), worsened in eight patients (Fig. 3b) and improved only in one (Fig. 3c). Overall, SV decreased  
252 from  $59.1 \pm 18.5$  ml to  $45.1 \pm 19.1$  ml, an average drop of 14 ml. Hence, the improvement gained in the  
253 systolic function after surgery was negated by a worsening diastolic function in most cases.

### 254 ***Predicted myofiber stress distribution***

255 Figure 4a shows the effect of surgery on the LV regional myofiber stress at end-systole in a representative  
256 patient. Before surgery, myofiber stress was highly inhomogeneous in the LV and was significantly  
257 elevated at the thin apical region where the infarct resides. After surgery, the decrease in LV size was  
258 accompanied by an increase in LV wall thickness, which led to a significant reduction in the peak  
259 myofiber stress. As a result, the myofiber stress distribution became more homogeneous after surgery.  
260 Figure 4b shows the peak myofiber stress in the LV before and after surgery in all 12 patients. Peak  
261 myofiber stress after SVR was substantially reduced in all patients regardless of whether this comparison  
262 was made with the peak myofiber stress found in the remote region of the pre-surgery LV or in the entire  
263 pre-surgery LV. On average, peak myofiber stress decreased by 50% (from  $141.2 \pm 45.1$  kPa to  $70.3 \pm$   
264  $15.0$  kPa) when compared to the remote region of the pre-surgery LV.

### 265 ***Predicted effects of left ventricular sphericity***

266 Figure 5 shows the effects of sphericity on the post-surgical LV model from Patient 1. Similar effects  
267 were also found in Patient 2 (not shown). Figure 5a shows the geometry of the post-surgical LV as it was  
268 “virtually elongated” (from the original post-surgery SI of 0.96 to an SI of 0.67) using the method  
269 described in the last paragraph of the section “Finite Element Modeling”. The LV cavity volume and the  
270 LV wall mass remained constant during this virtual “elongation” process. Figure 5b shows the ESPVR  
271 and EDPVR with SI as a parameter. As SI decreased, or equivalently, as the LV became more elongated,  
272 it became more compliant and diastolic function improved as a result. For patient 1,  $E_{ED}$  decreased  
273 moderately by about 6% (from 0.96 to 0.90 mmHg/ml, respectively) with a 30% decrease in SI. Roughly  
274 the same percentage of decrease in  $E_{ED}$  was also seen in patient 2 when SI decreased from 0.82 to 0.63.  
275 Similar to the effects of SI on diastolic function, systolic function also improved slightly as SI decreased.  
276 As SI decreased in Patient 1,  $E_{ES}$  increased slightly from 4.40 to 4.46 mmHg/ml and  $V_{o,ES}$  decreased  
277 from 53.1 to 50.6 ml. The same percentage of improvement in systolic function was also found in Patient

278 2 when SI decreased. The concurrent improvements in systolic and diastolic function were translated into  
279 an improvement in the Starling relationship (Fig. 5c). For an EDP between 4 to 20 mmHg, SV increased  
280 by about 3.5ml in both patients after a 30% reduction in SI. The diastolic and systolic function and the  
281 Starling relationship did not improve after further reduction of SI.

282 All the above-mentioned results were found to be relatively insensitive to a change in fiber angle  
283 distribution based on the repeated analysis (on one patient) using the recently acquired transmural linear  
284 variation of fiber angle from  $-42.4^\circ$  (epicardium) to  $35.7^\circ$  (endocardium).

## 285 Discussion

### 286 *Effects on stroke volume, systolic and diastolic function*

287 The improvement in systolic function after SVR was compromised by a concurrent decrease in the LV  
288 diastolic distensibility. This conclusion is broadly consistent with the speculation offered from the STICH  
289 trial (21) and the findings from clinical studies by Tulner et al. (34) and Brinke et al. (5), who observed  
290 similar effects of the surgery on EDPVR when invasive pressure-volume measurements were used  
291 directly after cardiopulmonary bypass (34) and six months after surgery (5). Specifically,  $K_{ED}$  was found  
292 to increase from  $0.021 \pm 0.009$  to  $0.037 \pm 0.021 \text{ ml}^{-1}$  after surgery in Tulner et al., and from  $0.012 \pm 0.003$   
293 to  $0.023 \pm 0.007 \text{ ml}^{-1}$  after surgery in Brinke et al. In the clinical study by Brinke et al., end-diastolic  
294 elastance  $E_{ED}$  (taken at 18 mmHg) was also found to have increased from  $0.15 \pm 0.08$  to  $0.24 \pm 0.10$   
295 mmHg/ml after surgery. Although our prediction of  $E_{ED}$  ( $0.48 \pm 0.15$  mmHg/ml and  $0.82 \pm 0.46$   
296 mmHg/ml at pre- and post-surgery, respectively) is larger than the measurements by Brinke et al., the  
297 percent increase is comparable. In terms of ESPVR, Tulner et al. found that  $E_{ES}$  improved from  $1.12 \pm$   
298  $0.63$  to  $1.57 \pm 0.55$  mmHg/ml, whereas Brinke et al. reported no significant change in  $E_{ES}$  ( $1.2 \pm 0.6$   
299 mmHg/ml) at six months after surgery. Although these values were also smaller than our prediction ( $2.40$   
300  $\pm 0.81$  mmHg/ml and  $3.93 \pm 2.20$  mmHg/ml before and after surgery), the percent improvement predicted  
301 by our mathematical models is comparable to that reported by Tulner et al.

302 As a result of the counteracting effects of surgery on ESPVR and EDPVR, our results show that  
303 the Starling relationship (or SV) was usually more depressed after surgery. This result is consistent with  
304 clinical findings (13, 22, 34, 39). The average decrease in SV found from these studies was about 7.5ml  
305 (compared to a decrease of 14 ml found here). In the clinical study by Brinke et al. (5), SV improved from  
306  $60 \pm 17$  to  $68 \pm 13$  ml six months after surgery.

### 307 ***Effects of a more ellipsoidal LV***

308 Our results show that the decrease in SV was also accompanied by an increase in SI after surgery. This  
309 finding is generally consistent with clinical findings, which show a decrease in SV (13, 22, 34, 39) and an  
310 increase in sphericity (12, 40) after SVR using endoventricular circular patch plasty. In contrast to what  
311 occurs after endoventricular circular patch plasty, the post-surgical LV was reported to have become more  
312 ellipsoidal when SVR was performed using septal anterior ventricular exclusion or Pacopexy technique  
313 (20). The values of SI reported here are larger than the values reported in Zhong et al. (40). This  
314 difference is because the short axis dimension was taken to be the widest LV minor axis at the  
315 endocardium based on a 4-chamber cine MRI view of the heart (40); whereas here, we have taken that  
316 dimension to be the maximum diameter of the MRI-reconstructed epicardial surface at the mid-ventricle.  
317 Our prediction that a decrease in SI can improve the diastolic and systolic function is also consistent with  
318 the theoretical studies by Choi et al. (9) and Geerts et al. (14). In these studies, an idealized prolate LV  
319 was used to show that the LV became more compliant during filling as it became more ellipsoidal (9), and  
320 the left ventricular pump function was reduced in a spherical LV when compared to an ellipsoidal LV  
321 (14). Given that the LV EDVs were smaller (around 80ml) in these studies than those found here (EDV =  
322  $176.9 \pm 58$  ml), the effects of sphericity appear to be size-independent, at least within the range of EDV  
323 mentioned here.

324 Our results show a decrease in SI by about 30% leads to an improvement in the Starling  
325 relationship of about a 3.5ml increase in SV. This result suggests that the post-surgical increase in SI  
326 contributes in part to the decrease in SV found after surgery. By restoring the LV SI back to its baseline

327 value (~ 30% lower than in post-surgery SI), we showed that the decrease in SV associated with an  
328 increase in sphericity cannot fully account for the 14ml post-surgical drop in SV. Therefore, it is likely  
329 that there are other mechanisms contributing to the decrease in SV other than the increased sphericity  
330 found after surgery.

### 331 ***Effects on myofiber stresses***

332 Our results show that the peak end-systolic myofiber stress decreased significantly after surgery in  
333 contrast to the compromised Starling relationship. Although the bulk wall stress can be predicted using  
334 Laplace's Law, prediction of the myofiber stress and its distribution within the LV requires mathematical  
335 modeling (38). These results are therefore more accurate in predicting LV remodeling (1, 15, 32) and  
336 regional oxygen consumption (30). Our results confirm that SVR can reduce peak myofiber stress (by  
337 50% on average), which can substantially reduce left ventricular myocardial oxygen consumption, MVO<sub>2</sub>  
338 (30). On the other hand, myofiber stress distribution may also become more homogeneous as a result of a  
339 more uniform ventricular wall thickness after surgery (right picture in Fig. 4a). Given that left ventricular  
340 remodeling is widely believed to be initiated by an increase in both magnitude and inhomogeneity of  
341 myofiber stress (1, 15, 32), the more homogeneous myofiber stress distribution found after surgery  
342 suggests that SVR + CABG may attenuate further adverse remodeling of the LV. Whether SVR can  
343 successfully restore myofiber stress level and distribution to those found in the normal human LV and  
344 help to prevent further adverse LV remodeling will require knowledge of the myofiber stress distribution  
345 in the normal human LV.

### 346 ***Limitations***

347 The limitations to our study are primarily due to the lack of acquired data. First, because MR images with  
348 delayed gadolinium enhancement were not available, infarcted regions in the LV were determined based  
349 on LV wall motion and were assumed to be transmural. As a result, other possible infarcted regions that

350 are less severe, particularly regions exhibiting hypokinesia, may have been omitted in our mathematical  
351 LV models.

352 Second, we were forced to assume physiologically reasonable values of 12 mmHg as EDP for all  
353 patients and the measured systolic blood pressure as ESP for individual patients because patient-specific  
354 left ventricular pressure data, which requires invasive measurements using micromanometer-tipped  
355 catheter, was not available. Left ventricular pressure, of course, tends to vary between patients. To  
356 overcome this limitation, we conducted sensitivity analysis to test whether our conclusions are affected by  
357 a variability in LV pressure. We have found that the conclusions are insensitive to a variation in LV  
358 pressure.

### 359 ***Conclusion***

360 In this first FE analysis of the effects of CABG+SVR based on patient-specific MR images, we have  
361 quantified the global and regional functional effects resulting from geometrical changes of the LV due to  
362 surgery. The three main conclusions from our computational analysis are as follows. First, LV systolic  
363 function improved whereas LV diastolic function worsened after SVR + CABG surgery. These  
364 conflicting effects resulted in a more depressed Starling relationship after surgery. Second, post-surgical  
365 increase in LV sphericity caused the stroke volume to decrease, even though this decrease is insufficient  
366 to compensate for the drop in stroke volume found after surgery. Third, the peak myofiber stress  
367 decreased substantially (50 %) and the myofiber stress distribution became more uniform in the LV after  
368 SVR + CABG surgery. These findings are consistent with the speculation proposed in the STICH trial  
369 (20) for the neutral outcome, that “the lack of benefit seen with surgical ventricular reconstruction is that  
370 benefits anticipated from surgical reduction of left ventricular volume (reduced wall stress and  
371 improvement in systolic function) are counter-balanced by a reduction in diastolic distensibility.” Since  
372 the results we presented are based on LV models reconstructed from patients at only one clinical center  
373 (Cleveland Clinic) who underwent a specific type of SVR (endoventricular circular patch plasty), they  
374 may not include the effects found when SVR is performed in other centers or when the surgery is

375 performed using other variants of SVR e.g., the Pacopexy technique (20), which may confer other  
376 benefits as described by Buckberg et al. (7). Since the outcome of SVR is still largely controversial, with  
377 both the European Society of Cardiology and European Association for Cardio-Thoracic Surgery  
378 recommending SVR (37) despite the negative outcome of Hypothesis 2 of the STICH trial (21), more  
379 models of other SVR variants using patient data from other clinical centers are needed to assess patient-  
380 specific efficacy of SVR.

381

## 382 **Acknowledgement**

383 This study was supported by the National Institutes of Health research grants: R01 HL077921 and R01  
384 HL086400 (JMG) and R01 HL063348, R01 HL084431 (MBR) and HL-084529 (GSK). This support is  
385 gratefully acknowledged.



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546 **Figure Captions**

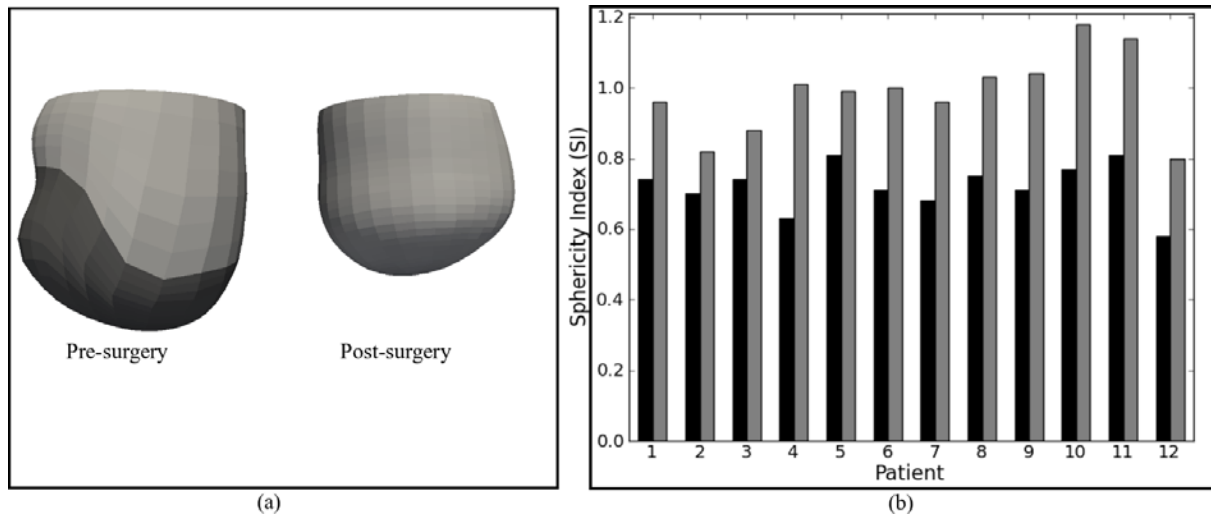
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549 the remote region, respectively. (b) Sphericity index (SI) of the 12 patients before  
550 surgery (dark color bars) and after surgery (light color bars).

551  
552 **Figure 2:** End-diastolic pressure-volume relationship (EDPVR) and end-systolic pressure-  
553 volume relationship (ESPVR) after surgery (Patient 1). Black line: Pre-surgery. Grey  
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555 from the different prescribed values of ESP and EDP. Dotted line: EDP = 4 mmHg  
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558  
559 **Figure 3:** Representative Starling relationship from three patients showing (a) no significant  
560 changes (Patient 1), (b) worsening (Patient 2), (c) improvement after surgery (Patient  
561 4). Dotted line: pre-surgery. Solid line: post-surgery. Bounds of the predicted Starling  
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563 post-surgery. These bounds were calculated from the EDPVR and ESPVR obtained by  
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568 right picture shows the stress in the more spherical post-surgery LV. (b) Peak end-  
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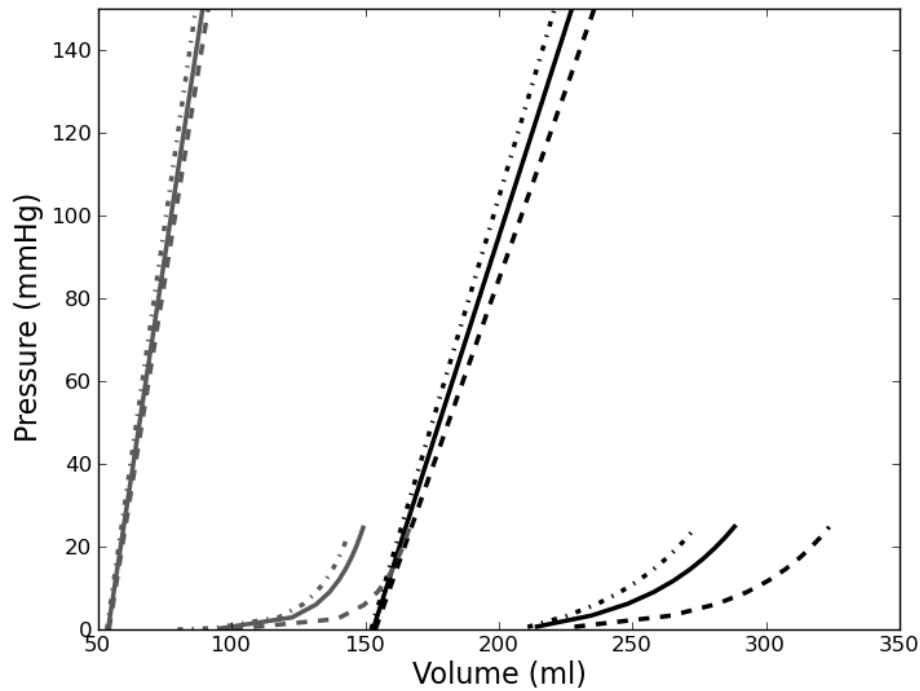
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579 **List of figures**

580

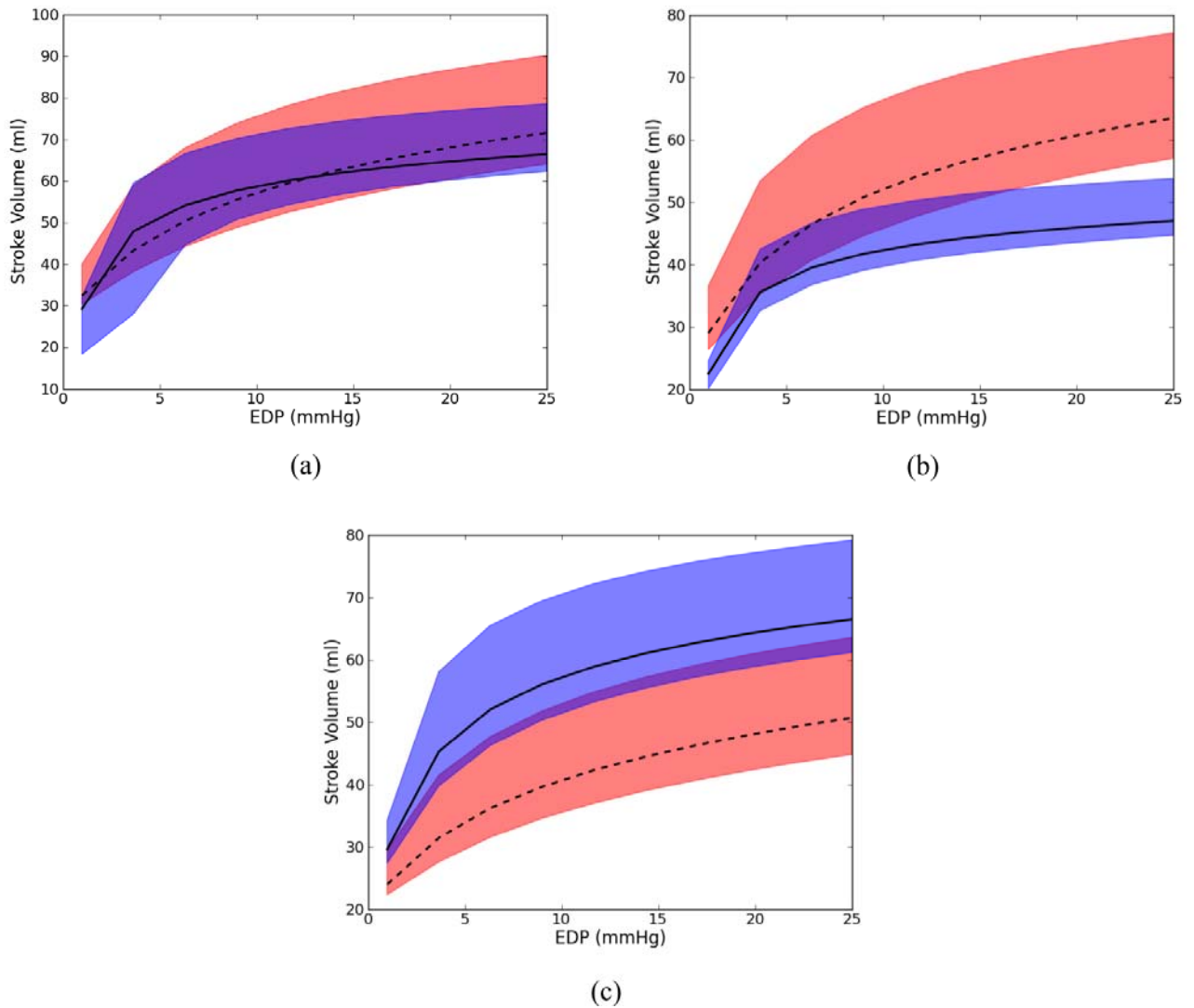
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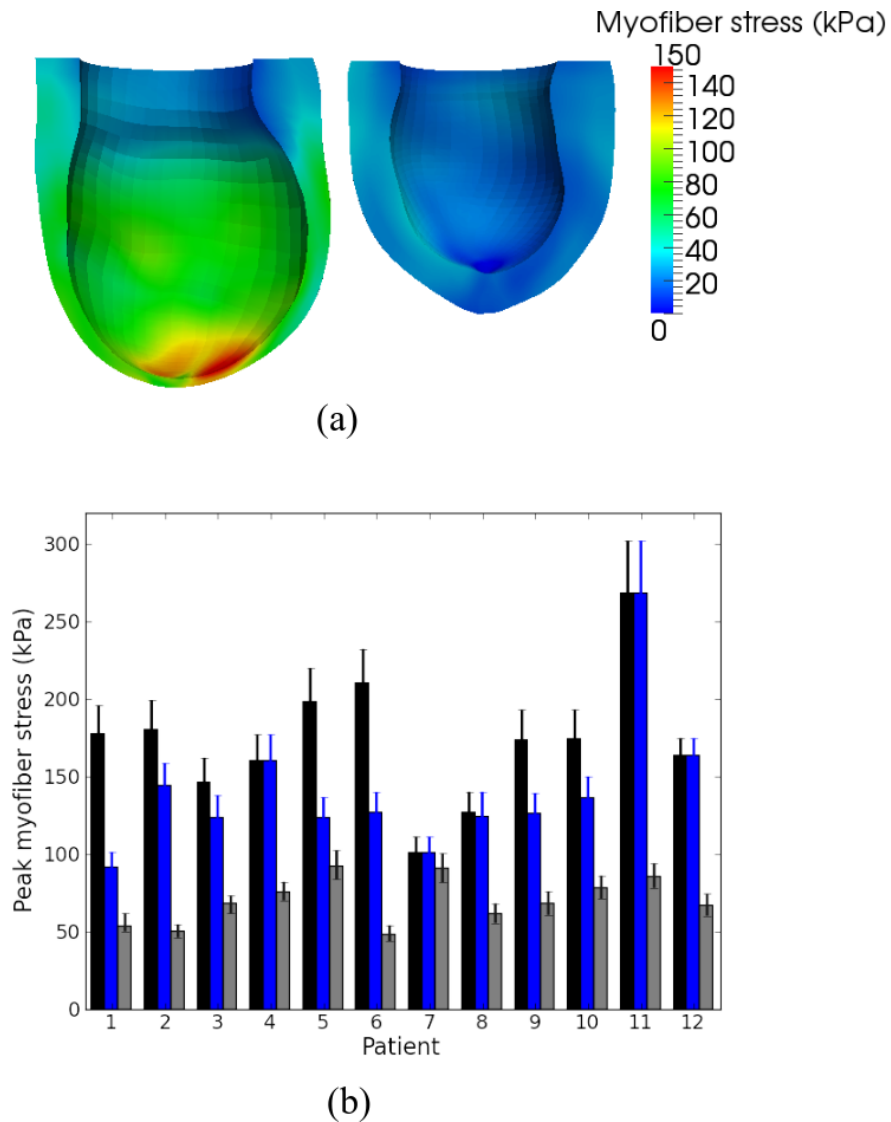
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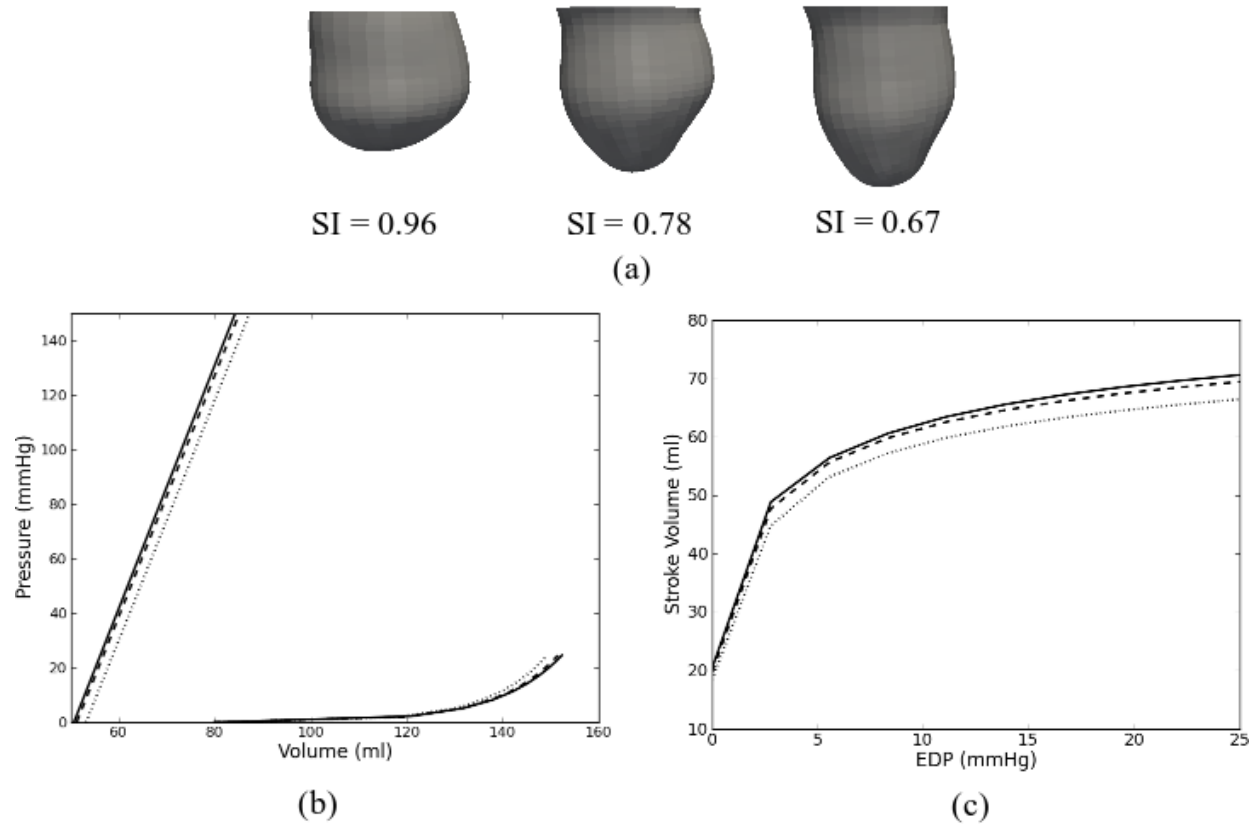
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599

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607 **Figure 5:** (a) LV with decreasing sphericity index (SI) from left to right. The original LV of Patient 1  
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 610 Dotted line (SI = 0.96), dashed line (SI = 0.78) and solid line (SI = 0.67).

## 611 **Appendix A.1: Constitutive law of the myocardial tissue**

612 Nearly incompressible, transversely isotropic, hyperelastic constitutive laws for passive (18) and active  
 613 myocardium (17) were used to model diastolic filling and active contraction. Passive material properties  
 614 were represented by the strain energy function:

$$615 \quad W = \frac{C}{2} \left\{ \exp \left[ b_f E_{11}^2 + b_t (E_{22}^2 + E_{33}^2 + E_{23}^2 + E_{32}^2) + b_{fs} (E_{12}^2 + E_{21}^2 + E_{13}^2 + E_{31}^2) \right] - 1 \right\}, \quad (\text{A.1})$$

616 where  $E_{11}$  is fiber strain,  $E_{22}$  is cross-fiber strain,  $E_{33}$  is radial strain,  $E_{23}$  is shear strain in the transverse  
 617 plane, and  $E_{12}$  and  $E_{13}$  are shear strain in the fiber-cross fiber and fiber-radial planes, respectively. Values  
 618 for the material constants  $b_f$ ,  $b_t$ , and  $b_{fs}$  were obtained from large animal studies and have values 49.25,  
 619 19.25 and 17.44 respectively (33). The material constant  $C$  was adjusted until the LV end-diastolic  
 620 volumes matched the experimentally measured values as described in the main text.

621 Active contraction was modeled by defining the total stress as the sum of the passive stress  
 622 derived from the strain energy function  $W$  and an active fiber directional component,  $\mathbf{T}_0$ , which is a  
 623 function of time,  $t$ , peak intracellular calcium concentration,  $Ca_0$ , sarcomere length,  $l$ , and maximum  
 624 isometric tension achieved at the longest sarcomere length,  $T_{\max}$  (17) i.e.

$$625 \quad \mathbf{S} = p J \mathbf{C}^{-1} + 2 J^{-2/3} \text{Dev} \left( \frac{\partial \tilde{W}}{\partial \tilde{\mathbf{C}}} \right) + \mathbf{T}_0(t, Ca_0, l, T_{\max}), \quad (\text{A.2})$$

626 In Eq. (A.2),  $\mathbf{S}$  is the second Piola-Kirchoff stress tensor,  $p$  is the hydrostatic pressure introduced as the  
 627 Lagrange multiplier needed to ensure incompressibility,  $J$  is the Jacobian of the deformation gradient  
 628 tensor,  $\mathbf{C}$  is the right Cauchy-Green deformation tensor,  $\tilde{\mathbf{C}}$  is the deviatoric decomposition of  $\mathbf{C}$  (i.e.  
 629  $\mathbf{C} = J^{2/3} \tilde{\mathbf{C}}$ ),  $\tilde{W}$  is the deviatoric contribution of the strain energy function  $W$  given in Eq. (A.1) and Dev is  
 630 the deviatoric projection operator defined as

$$631 \quad \text{Dev}(\bullet) = (\bullet) - \frac{1}{3} \left( [\bullet] : \mathbf{C} \right) \mathbf{C}^{-1}. \quad (\text{A.3})$$

632 Assumption of near incompressibility of the myocardium also requires the decoupling of the strain energy  
 633 function  $W$  into its dilational  $U$  and deviatoric components  $\tilde{W}$ , i.e.

$$634 \quad W = U(J) + \tilde{W}(\tilde{\mathbf{C}}). \quad (\text{A.4})$$

635 The active fiber-directed stress component is defined by a time-varying elastance model, which at end-  
 636 systole, is reduced to

$$637 \quad T_0 = \frac{1}{2} T_{\max} \frac{Ca_0^2}{Ca_0^2 + ECa_{50}^2} \left( 1 - \cos \left( \frac{0.25}{m l_R \sqrt{2 E_{11} + 1} + b} + 1 \right) \pi \right). \quad (\text{A.5})$$

638 In Eq. (A.5),  $m$  and  $b$  are material constants, and  $ECa_{50}$  is the length-dependent calcium sensitivity given  
 639 by

$$640 \quad ECa_{50} = \frac{(Ca_0)_{\max}}{\sqrt{\exp \left[ B \left( l_R \sqrt{2 E_{11} + 1} - l_0 \right) \right] - 1}}, \quad (\text{A.6})$$

641 where  $B$  is a constant,  $(Ca_0)_{\max}$  is the maximum peak intracellular calcium concentration,  $l_0$  is the  
 642 sarcomere length at which no active tension develops and  $l_R$  is the stress-free sarcomere length. Material  
 643 constants for active contraction were taken to be (33):  $Ca_0 = 4.35 \mu\text{mol/L}$ ,  $(Ca_0)_{\max} = 4.35 \mu\text{mol/L}$ ,  $B =$   
 644  $4.75 \mu\text{m}^{-1}$ ,  $l_0 = 1.58 \mu\text{m}$ ,  $m = 1.0489 \text{ sec } \mu\text{m}^{-1}$ ,  $b = -1.429 \text{ sec}$ , and  $l_R = 1.85 \mu\text{m}$ . Based on biaxial  
 645 stretching experiments, cross-fiber, in-plane active stress equivalent to 40% of that along the myocardial  
 646 fiber direction was also added. Determination of the patient-specific material parameter  $T_{\max}$  is described  
 647 in the main text.