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1 Human cardiac function simulator for the optimal design of
2 a novel annuloplasty ring with a sub-valvular element for
3 correction of ischemic mitral regurgitation

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40 Abstract

41 Purpose: Ischemic mitral regurgitation is associated with substantial risk of death. We sought to:
42 (1) detail significant recent improvements to the Dassault Systèmes human cardiac function
43 simulator (HCFS); (2) use the HCFS to simulate normal cardiac function as well as pathologic
44 function in the setting of posterior left ventricular (LV) papillary muscle infarction; and (3) debut
45 our novel device for correction of ischemic mitral regurgitation.

46 Methods: We synthesized two recent studies of human myocardial mechanics. The first study
47 presented the robust and integrative finite element HCFS. Its primary limitation was its poor
48 diastolic performance with an LV ejection fraction below 20% caused by overly stiff ex-vivo
49 porcine tissue parameters. The second study derived improved diastolic myocardial material
50 parameters using in-vivo MRI data from five normal human subjects. Combining these models,
51 ischemic mitral regurgitation was simulated by computationally infarcting an LV region including
52 the posterior papillary muscle. Contact between our novel device and the mitral valve apparatus
53 was simulated using Dassault Systèmes SIMULIA software.

54 Results: Incorporating improved cardiac geometry and diastolic myocardial material properties
55 in the HCFS resulted in a realistic LV ejection fraction of 55%. Simulating infarction of posterior
56 papillary muscle caused regurgitant mitral valve mechanics. Implementation of our novel device
57 corrected valve dysfunction.

58 Conclusions: Improvements in the current study to the HCFS permit increasingly accurate study
59 of myocardial mechanics. The first application of this simulator to abnormal human cardiac
60 function suggests that our novel annuloplasty ring with a sub-valvular element will correct
61 ischemic mitral regurgitation.

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63

64 **Keywords:** finite element method; realistic simulation; myocardial infarction; ventricular

65 function; Ischemic mitral regurgitation; mitral annuloplasty

66

67 Introduction

68 Ischemic mitral regurgitation is a consequence of adverse left ventricular (LV) remodeling after
69 myocardial injury, in which there is enlargement of the LV chamber and mitral annulus, apical
70 and lateral migration of the papillary muscles, leaflet tethering, and reduced coaptation area.
71 These processes lead to malcoaptation of the leaflets and consequently mitral insufficiency. The
72 leaflets themselves are normal, and the disease occurs in the myocardium rather than in the
73 valve itself [1]. Despite this, beyond medical therapy, surgical correction of mitral regurgitation
74 has largely relied upon native valve repair or valve replacement. A recent randomized clinical
75 trial [1] found no significant difference in LV reverse remodeling or survival at 12 months
76 between patients who underwent mitral-valve repair with ring annuloplasty and those who
77 underwent mitral-valve replacement. Replacement provided a more durable correction however,
78 with mitral regurgitation recurring less than 1/10th as often at 12 months compared to outcomes
79 of valve repair. We hypothesize that mitral-valve repair using a novel annuloplasty ring with a
80 sub-valvular element would provide a more effective treatment of ischemic mitral regurgitation
81 than mitral-valve repair using a standard annuloplasty ring. Our rationale is that the sub-valvular
82 element engages the chordae of the posterior leaflet, and contacts the inferior free edge of said
83 leaflet. As a consequence, it counterbalances an apical and lateral shifting of the coaptation line
84 in patients with ischemic cardiomyopathy, thus reestablishing proper leaflet coaptation and
85 valve function.

86 Computational modeling is one way to systematically assess the effects of pathology and
87 proposed surgical repair on heart function [2]. By simulating the effect of disease or injury on the
88 heart, simulations allow investigators to explore a variety of pathologic conditions that would be
89 difficult to consistently create in-vivo [3]. Models also have an important role in cardiac device

90 design, as application of myriad treatment designs to identical pathology allows for natural
91 isolation of treatment effects [4,5]. However, current models of cardiac function are limited by
92 assumptions related to geometry and material properties, and importantly, none have been fully
93 validated with detailed experimental data [6]. Dassault Systèmes SIMULIA recently launched
94 the Living Heart Project to develop an integrated physics-based simulator of cardiac physiology.
95 The Living Heart model or Human Cardiac Function Simulator (HCFS) not only includes the
96 entire heart—all four chambers, valves and major vessels—but also includes the
97 electrophysiology and fibrous architecture of the myocardium. There is increasing evidence that
98 this model can be used to predict the progression of pathology, the outcome of surgical repair
99 and the use of cardiac devices. We recently published a proof-of-concept methods paper using
100 this model to simulate the normal human heart [7]. Although groundbreaking, the initial model
101 had some limitations. Most importantly, the LV ejection fraction was only 19%, much lower than
102 the normal range at rest ($62.3 \pm 6.1\%$) as assessed using radionuclide angiography [8]. In
103 the current study, we simulated a physiologically normal LV ejection fraction by using more
104 realistic heart geometry and diastolic myocardial material properties than those proposed in the
105 earlier proof-of-concept paper [7].

106 In this invited article concerned with mitral valve function, pathology and therapeutic options, we
107 therefore seek to: (1) detail our significant improvements in the geometry and diastolic material
108 properties of the Dassault Systèmes HCFS; (2) use the resulting more realistic model to
109 simulate normal cardiac function as well as abnormal cardiac function due to a myocardial
110 infarction that includes the posterior LV papillary muscle; and (3) use the abnormal human heart
111 model to debut a novel annuloplasty ring with a sub-valvular element for correction of ischemic
112 mitral regurgitation.

113

114

115 Materials and Methods

116 *Human Cardiac Function Simulator*

117 We refer the interested reader to Section 2 of Baillargeon et al [7] for our continuum model of
118 electro-mechanical coupling based on the kinematic equations, the balance equations, and the
119 constitutive equations. In Section 3 of that methods paper, we illustrate our computational
120 model, based on the strong and weak forms of the governing equations, their temporal and
121 spatial discretizations, their linearizations, and the handling of internal variables. In the present
122 study, we use a more realistic solid model of the human heart (**Figure 1**).

123 The Solid Zygote 3D Heart geometries for computer-aided design (CAD) and simulation were
124 created by Zygote Media Group, Inc. (UT, USA). Generation I of the Solid Zygote Heart
125 geometry (the one we used in [7]) was developed using medical imaging data from a single
126 human subject in 2005. An 8-slice GE Light Speed CT platform was used to acquire 5mm axial
127 slices, with an imaging matrix of 512x512. Generation II of the Solid Zygote Heart geometry (the
128 one used in the current study) was created by the Zygote Media Group in 2013, using improved
129 imaging techniques. A 64-slice GE Light Speed scanner, using retrospective ECG gating and
130 achieving a slice thickness of 0.75mm with 512x512 imaging matrix, acquired images of an
131 anonymous healthy middle-aged Caucasian male. Imaging data was resampled to twice the
132 voxel density in each dimension, reformatted into standard cardiac imaging views, and was
133 manually segmented to create a rough polygonal geometry. This rough geometry was then
134 cleaned of noise, artifacts, and anomalies using standard 3D editing software
135 (Symbolics/Nichiman Graphics/Mirai, Wavefront, 3D Studio/3D Studio Max, Alias Power

136 Animator, Maya, Cinema 4D, Focus, Amira, and SolidWorks). Just as for the first generation
137 Solid Zygote 3D Heart, certain anatomic elements (e.g. papillary muscles, valves, and chordae
138 tendineae) had to be added to the model manually, as their fine detail could not be captured
139 well with clinical imaging technology. In the same respect, the finest geometric details of certain
140 anatomical structures (e.g. trabeculae carneae) were simplified so as to avoid an unnecessarily
141 complex and computationally demanding model. It is important to note here that the Generation
142 II Solid Zygote Heart geometry is a component of a larger anatomical collection that includes
143 integrated anatomical geometries of a 50th percentile (U.S.) male and hence, there are no
144 “patient-specific” anatomical features of the heart model.

145 **Figure 2** shows the electrical finite element model of Zygote’s second-generation solid heart
146 geometry discretized with 449,560 linear tetrahedral elements, 655 1D linear conduction
147 elements, 103,770 nodes, and 103,770 electrical degrees of freedom. The model depicted in
148 that figure was created using Abaqus CAE. **Figure 3** shows how the 655 1D linear electrical
149 conduction elements are distributed between the left and right ventricles. **Figure 4** shows the
150 mechanical finite element model of the human heart discretized with 449,560 linear tetrahedral
151 (C3D4) elements, 12,915 linear quadrilateral shells, 7577 linear triangular (S4R reduced
152 integration) shells, 636 linear truss (T3D2) elements, 16,824 rigid triangular elements, 130,290
153 nodes, and 443,564 mechanical degrees of freedom. The S4R is the only element type with
154 hourglass control (based on enhanced strain). Otherwise, the muscle fiber model, the fluid
155 model, and most of the model parameters in the current study are as described in Section 4 of
156 Baillargeon et al [7].

157 The only non-valvular model parameters used in the current study that differ from those in Table
158 1 of Baillargeon et al [7] relate to the passive material properties of myocardium, and are as
159 follows: $k = 1,000$ kPa; $a = 0.33$ kPa; $b = 7.08$; $a_{ff} = 0.25$ kPa; $b_{ff} = 5.34$; $a_{ss} = 0$; $b_{ss} = 0$; $a_{fs} = 0$;
160 $b_{fs} = 0$. Our rationale for modifying these parameters is to correct the non-physiologic LV

161 ejection fraction of the first generation HCFS. In Baillargeon et al [7], we used model parameter
162 values from the literature (see references listed in their Table 1) concerning electrical,
163 mechanical, and electro-mechanical phenomena and flow in the heart and modified unknown
164 model parameter values concerning circulation in order to simulate an LV pressure-volume loop.
165 The resulting LV pressures and shape of the loop in Figure 10 of that study are realistic, but the
166 LV volumes are not indicative of a normal human heart. Specifically, end-diastolic and end-
167 systolic volumes were 103 and 83 mL, respectively, corresponding to a stroke volume of 20 mL
168 and an ejection fraction of only 19.4% (= 20 mL divided by 103 mL). In a recent study by Genet
169 et al [5] five normal human subject-specific LV models were created, with an average ejection
170 fraction of $56 \pm 3.95\%$. The passive mechanical model parameter values used in the current
171 study were obtained by fitting the passive mechanical behavior under shearing deformation
172 obtained from the constitutive model for the normal myocardium in Appendix A of Genet et al
173 [5]. **Figure 5** shows a comparison of passive mechanical behavior under shearing deformation
174 between the human heart model of Baillargeon et al [7] and the one used in the current study.

175 Since the current study was mainly concerned with mitral valve function, pathology and
176 therapeutic options, additional attention was given to the mechanical properties of the leaflets
177 and chordae. **Figure 6** shows the fit of model parameter values defining leaflet circumferential
178 and radial stress-strain relationships to measurements from the study of May-Newman and Yin
179 [9]. Thus, porcine data was used to simulate human mitral tissue. Similarly, **Figure 7** shows the
180 fit of model parameter values defining chordae basal and marginal stress-strain relationships to
181 measurements from the study of Kunzelman and Cochran [10]. In both cases, the Dassault
182 Systèmes SIMULIA optimization software Isight was used to minimize least-squared differences
183 between measured and predicted stresses at matching strains.

184 ***Human Cardiac Function Simulator with LV Myocardial Infarction***

185 The state-of-the-art whole human heart model described above was then modified in the most
186 straightforward manner to simulate regurgitant mitral valve mechanics. This modification
187 involved creating an LV region that included the posterior papillary muscle. The myocardial
188 material properties in that region were modified to ensure that no active myocardial stress was
189 generated at any time during the cardiac cycle, thus simulating infarction. **Figure 8** shows the
190 LV region in which active myocardial stress development was suppressed.

191

192 ***Novel Device for Correction of Ischemic Mitral Regurgitation***

193 A recent randomized clinical trial [1] confirmed an excess of incidence of recurrence of mitral
194 regurgitation at 1 year among patients undergoing mitral-valve repair. The type of annuloplasty
195 ring was chosen according to the preference of the surgeon. The protocol mandated the use of
196 an approved rigid or semi-rigid complete annuloplasty ring, which was downsized for the
197 annulus diameter. In collaboration with the Cleveland Clinic (OH, USA) we created a prototype
198 undersized annuloplasty ring with a sub-valvular element shown in **Figure 9a**. To the best of our
199 knowledge, it is the first annuloplasty ring to include a sub-valvular element. Our rationale is that
200 the sub-valvular element engages the chordae of the posterior leaflet, and contacts the inferior
201 free edge of said leaflet. As a consequence, it counterbalances an apical and lateral shifting of
202 the coaptation line in patients with ischemic cardiomyopathy, thus reestablishing proper leaflet
203 coaptation and valve function. We created a rigid finite element representation of this novel
204 device, which is shown in **Figure 9b**. The device was modeled as rigid for simplicity. **Figure 10a**
205 is a close-up view of the whole heart model with the left atrium removed. **Figure 10b** clearly
206 illustrates the computational geometry of our novel device in contact with the mitral valve
207 apparatus. Tight, frictionless contact between the device and the mitral valve annulus was
208 activated at numerous points that represented sutures. It is important to point out here that there
209 was separation contact (separation was allowed); a standard penalty-based contact algorithm
210 was used.

211 **Results**

212 The more realistic geometry of the Generation II Solid Human heart model, and improved
213 diastolic myocardial material properties caused LV ejection fraction to increase from 19.4% to
214 55%. **Figure 11** shows normal LV behavior predicted by this model. Additionally, the model

215 predicted maximum long-axis shortening of 12.1 mm, which is in agreement with the
216 measurements (12.2 ± 3.8 mm) of Rogers et al [11]. **Figure 12** shows close-up views of the
217 second generation HCFS with the left atrium removed to clearly show the mitral valve in its open
218 and closed states during the cardiac cycle. **Movie 1** shows the same view but with the mitral
219 valve in action throughout the cardiac cycle. To induce regurgitant mitral valve mechanics, the
220 size of the infarcted LV region was iteratively increased until the LV ejection fraction decreased
221 from 55% to 45%. The effect of myocardial infarction on the LV pressure-volume loop is shown
222 in **Figure 13**. Creating the infarcted LV region also resulted in decreased mitral valve leaflet
223 coaptation (**Figure 14**). This is shown dynamically in **Movie 2**. Simulation of the annuloplasty
224 ring with the sub-valvular component resulted in an increase in mitral valve coaptation in the
225 area originally affected by the LV infarction. **Figure 15** shows a close-up view of the model with
226 the left atrium removed to clearly illustrate this. **Movie 3** shows the same view but with the mitral
227 valve in contact with our novel device throughout the cardiac cycle. The simulation was made
228 with a rigid (flat plane) annuloplasty ring and sub-valvular element, and thus, device stresses
229 and strains cannot be extracted from the analysis. In our opinion, another consequence of using
230 that particular rigid annuloplasty ring is that a non-negligible regurgitant area characterized the
231 post-annuloplasty configuration in the A1-P1 region in Movie 3. On the other hand, we were
232 able to extract average forces (**Figure 16**) in the chordae between the posterior mitral valve
233 leaflet and the posterior LV papillary muscle during the cardiac cycle for the three cases (i.e.,
234 healthy heart, heart with an LV myocardial infarction, and diseased heart treated with our novel
235 device). Following LV myocardial infarction peak average chordae force became 85% of that in
236 the healthy heart. Treatment of the diseased heart with our novel device caused peak average
237 chordae force to reduce further (to 72% of that in the healthy heart).

238

Discussion

239 Our study details three significant advancements in realistic simulation of human cardiac
240 function, pathology and therapeutic options, for the entire heart. First, incorporating improved
241 cardiac geometry and diastolic myocardial material properties in the Dassault Systèmes human
242 cardiac function simulator (HCFS) caused LV ejection fraction to increase from 19% to a more
243 physiological value of 55%. Second, simulating infarction of the posterior LV papillary muscle
244 caused regurgitant mitral valve mechanics; a pathologic state associated with a substantial risk
245 of death [1]. Third, implementation of our undersized annuloplasty ring with a sub-valvular
246 element corrected valve dysfunction. Figure 10 clearly shows the impact of our novel device; the
247 engagement of the chordae causes the posterior leaflet to move forward, which ultimately
248 causes improved coaptation of the valve leaflets during ventricular systole. Moreover, our
249 results suggest that virtual valve repair, in combination with nonlinear programming tools, e.g.,
250 the Dassault Systèmes Abaqus software in conjunction with Isight, can be used to optimize the
251 design of novel devices for correction of ischemic mitral or tricuspid regurgitation. Lastly, the
252 simulations could be repeated with a deformable annuloplasty ring and sub-valvular element,
253 and fatigue-simulation software to make durability predictions.

254 The most effective surgical approach for treating severe ischemic mitral regurgitation remains
255 controversial [1]. In the past few years, the use of mitral-valve repair has greatly exceeded the
256 use of replacement [12]. However, no randomized trials have established the superiority of
257 repair across a spectrum of patients with severe ischemic mitral regurgitation [1]. In their
258 correspondence, Gorman et al [13] point out that there was substantial reverse remodeling
259 among the patients in the repair group in [1] who did not have recurrent moderate or severe
260 mitral regurgitation. They propose that all patients should undergo repair and that those in
261 whom postoperative moderate or severe mitral regurgitation develops should undergo

262 secondary percutaneous mitral-valve replacement. According to Acker et al [14], a less
263 speculative and less aggressive approach would be to use predictive models of recurrent mitral
264 regurgitation, and, in patients with a high likelihood of recurrence, to use replacement or a more
265 complex repair technique that specifically addresses leaflet tethering.

266 Ours is the second study to be performed as part of the Living Heart Project. The first [7], which
267 presented a proof-of-concept simulator for a four-chamber human-heart model created from
268 computed tomography and MRI data, illustrated the governing equations of excitation-
269 contraction coupling and discretized them using an explicit finite element environment
270 (Abaqus/explicit) [7]. To illustrate the basic features of their model, the authors visualized the
271 electrical potential and mechanical deformation across the human heart throughout its cardiac
272 cycle. Nine parameters defined the orthotropic passive myocardial response as measured in
273 excised porcine myocardium by Dokos et al [15], resulting in an LV ejection fraction of 19.4%. In
274 the present study, we used five different passive mechanical parameter values to define
275 transverse isotropy with respect to the local myofiber direction as observed in the LVs of five
276 normal human subjects, with a resultant ejection fraction of 55%. It might seem quite surprising
277 that these two sets of model parameters (both supposedly representing normal mammalian
278 passive myocardial mechanical properties) predict such different LV ejection fractions. The most
279 likely explanation for this discrepancy is that the excised porcine myocardium studied by Dokos
280 and co-workers was abnormally stiff (in contracture). This seems to indicate that material
281 parameters determined or estimated from in-vivo clinical or experimental data predict cardiac
282 mechanics more realistically than those directly measured from ex-vivo experimental data.

283 Ours is one of the few finite element modeling studies to include the mitral valve and the LV.
284 The first finite element model of the LV with mitral valve [16] did not include the right ventricle or
285 either atrium. In that study, the authors expanded their previous finite element models of the LV
286 to incorporate the leaflets and chordae of the mitral valve based on drawings of the ex-vivo

287 ovine mitral apparatus. Their LV model was based on MRI data from a sheep that developed
288 moderate ischemic mitral regurgitation after postero-basal myocardial infarction. They
289 demonstrated the utility and power of their finite element model by using it to test the hypothesis
290 that a reduction in the stiffness of the ischemic region will decrease dyskinesis of the posterior
291 LV wall, increase the displacement of the posterior papillary muscle and thereby increase
292 ischemic mitral regurgitation. However, in that study, the leaflets were not modeled to include
293 contact, which resulted in spurious penetration of the anterior leaflet into the posterior leaflet.
294 That limitation was corrected in a subsequent study of the effect of annuloplasty ring shape in
295 ischemic mitral regurgitation [17][18]. That study concluded that the effects of saddle shaped
296 and asymmetric mitral annuloplasty rings are similar. This conclusion begs the question as to
297 why are there so many different mitral annuloplasty rings available to cardiac surgeons and
298 more importantly, on what basis have they been designed [19,20].

299

300 ***Study Limitations and Future Directions***

301 In our study, we made significant improvements in cardiac geometry and diastolic myocardial
302 material properties in the Dassault Systèmes HCFS. There is still much opportunity for added
303 realism in the HCFS, however. Our ultimate goal is to replace the compartment approach to the
304 fluids portion of the simulation with a resolved 3D fluid dynamics solution. A fully coupled fluid-
305 structure interaction (FSI) model of the human heart is highly desirable, albeit hugely
306 challenging, and the major focus of research for numerous investigators. Kunzelman and co-
307 workers [2,3,6] are utilizing an advanced FSI model of the mitral valve system that allows
308 analysis of the valve in the normal, diseased, or repaired states. Their findings are validated by
309 utilizing a well-established, but unique experimental in-vitro system in which mitral valve function
310 can be extensively assessed. Once fully validated, their FSI model can be used to explore and
311 compare various types of valvular pathology and repair. The long-term goal of their research is
312 to provide an advanced FSI model of the mitral valve that could ultimately be used for
313 individualized patient planning for mitral valve repair.

314 Including flow analysis like that mentioned above, would allow us to predict shear stresses on
315 the myocardial wall, and more importantly, on the four heart valves, through the entire cardiac
316 cycle. Such an approach presents tremendous opportunities to better understand the
317 mechanisms of valvular disease and optimize treatment in the form of valve repair or
318 replacement, either through open heart surgery or minimally invasive intervention. Despite the
319 limited treatment of fluids in the current analysis, we are confident that our novel annuloplasty
320 ring with a sub-valvular element will provide durable correction of ischemic mitral regurgitation
321 because of (unpublished) promising long-term outcomes data from treated sheep.

322 ***Conclusion***

323 In conclusion, this study incorporated improved cardiac geometry and diastolic myocardial
324 material properties in the Dassault Systèmes HCFS, which resulted in a realistic LV ejection
325 fraction of 55%. Simulating infarction of the posterior LV papillary muscle predicted regurgitant
326 mitral valve mechanics. Implementation of our undersized annuloplasty ring with a sub-valvular
327 element corrected valve dysfunction. Our experience suggests that valve repair can be further
328 optimized with additional software (e.g., fatigue, optimization) to develop novel annuloplasty
329 rings with sub-valvular elements for correction of ischemic mitral or tricuspid regurgitation.

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340

341 **Disclosures**

342 Brian Baillargeon and Nuno Rebelo are employees of Dassault Systèmes Simulia Corporation,
343 Fremont, CA, USA.

344 **Statement of Human Studies**

345 Not applicable. As detailed in the Materials and Methods section, we used a Solid Zygote 3D
346 Heart geometry created by Zygote Media Group. We did not acquire the images.

347 **Statement of Animal Studies**

348 Not applicable.

349

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403

404 Figure captions

405 Figure 1: Solid model of the human heart used as the basis for our improved model. It was
406 created from computed tomography and magnetic resonance imaging; adapted with permission
407 from (Zygote Media Group and Inc., 2014).

408 Figure 2: Electrical finite element model of the human heart discretized with 449,560 linear
409 tetrahedral elements, 655 1D linear conduction elements, 103,770 nodes, and 103,770
410 electrical degrees of freedom. Red elements comprise the atria; blue elements comprise the
411 ventricles.

412 Figure 3: Representation of the 655 1D linear electrical conduction elements in the LV (red) and
413 RV (blue) used in the HCFS.

414 Figure 4: Mechanical finite element model of the human heart discretized with 449,560 linear
415 tetrahedral elements, 12,915 linear quadrilateral shells, 7577 linear triangular shells, 636 linear
416 truss elements, 16,824 rigid triangular elements, 130,290 nodes, and 443,564 mechanical
417 degrees of freedom.

418 Figure 5: Comparison of passive mechanical behavior under shearing deformation between the
419 human heart model of Baillargeon et al (2014) and that used in the current study. “FN” stands
420 for shear in the fiber-normal plane. “FS” stands for shear in the fiber-sheet plane. True (Cauchy)
421 stress and true (logarithmic) strain are plotted in this figure.

422 Figure 6: Fit of leaflet stress-strain relationships (red indicates circumferential, blue indicates
423 radial) to experimental data. "Exp" stands for experimental. True (Cauchy) stress and true
424 (logarithmic) strain are plotted in this figure.

425 Figure 7: Fit of chordae stress-strain relationships to experimental data. Red line indicates basal
426 chordae; blue line indicates marginal chordae. "Exp" stands for experimental. True (Cauchy)
427 stress and true (logarithmic) strain are plotted in this figure.

428 Figure 8: Ischemic mitral regurgitation was simulated by preventing active myocardial stress to
429 be developed in an LV region (shown in red). Left: view of whole heart model; Right: close-up
430 view of infarcted LV region showing endocardial surface and posterior papillary muscle.

431 Figure 9: Novel annuloplasty ring with a sub-valvular element for correction of ischemic mitral
432 regurgitation. A: photograph of actual prototype; B: finite element model of prototype.

433 Figure 10: A: Close-up view of whole heart model with left atrium removed. Sutures attaching
434 the novel device to the mitral valve annulus are shown in pink. B: Side views showing finite
435 element model of novel device in contact with mitral valve apparatus.

436 Figure 11: Plots showing normal human heart behavior. A: LV pressure-volume loop; B: LV
437 long-axis shortening versus time.

438 Figure 12: Close-up views of whole heart model with left atrium removed to clearly show mitral
439 valve in its open (left) and closed (right) states during the cardiac cycle.

440 Figure 13: Effect of myocardial infarction (blue line) on LV pressure-volume loop. The red line
441 indicates no myocardial infarction.

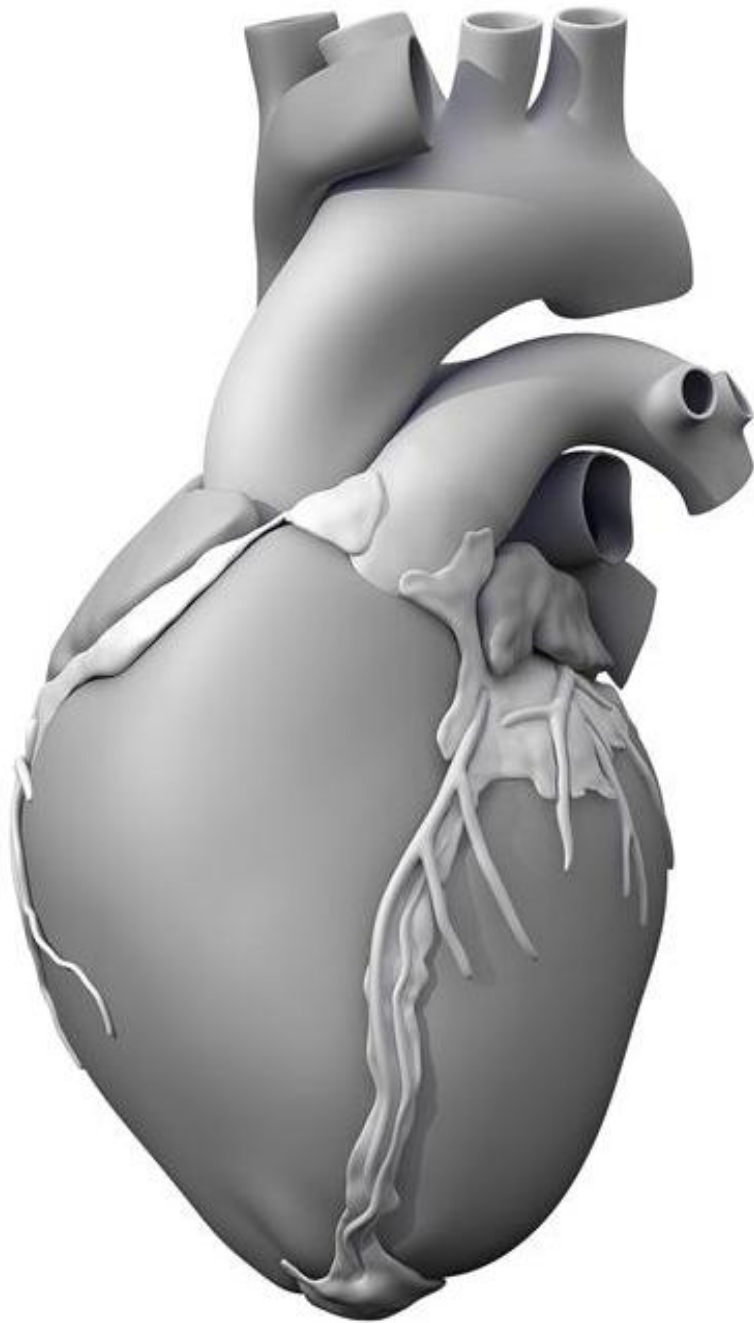
442 Figure 14: Effect of infarcted LV region on mitral valve leaflet coaptation. Left: view of entire
443 mitral valve; Right: close-up view of affected area.

444 Figure 15: Close-up view of the mitral valve in the whole heart model with a simulated infarcted
445 LV region. The left atrium was removed to clearly show how the simulated novel device
446 increases mitral leaflet coaptation.

447 Figure 16: Average forces in chordae between the posterior mitral valve leaflet and the posterior
448 LV papillary muscle during the cardiac cycle. The force time courses were normalized by the
449 peak average chordae force value in the healthy heart (red curve). Also shown are the cases of
450 LV myocardial infarction (blue curve) and diseased heart treated with our novel device (green
451 curve).

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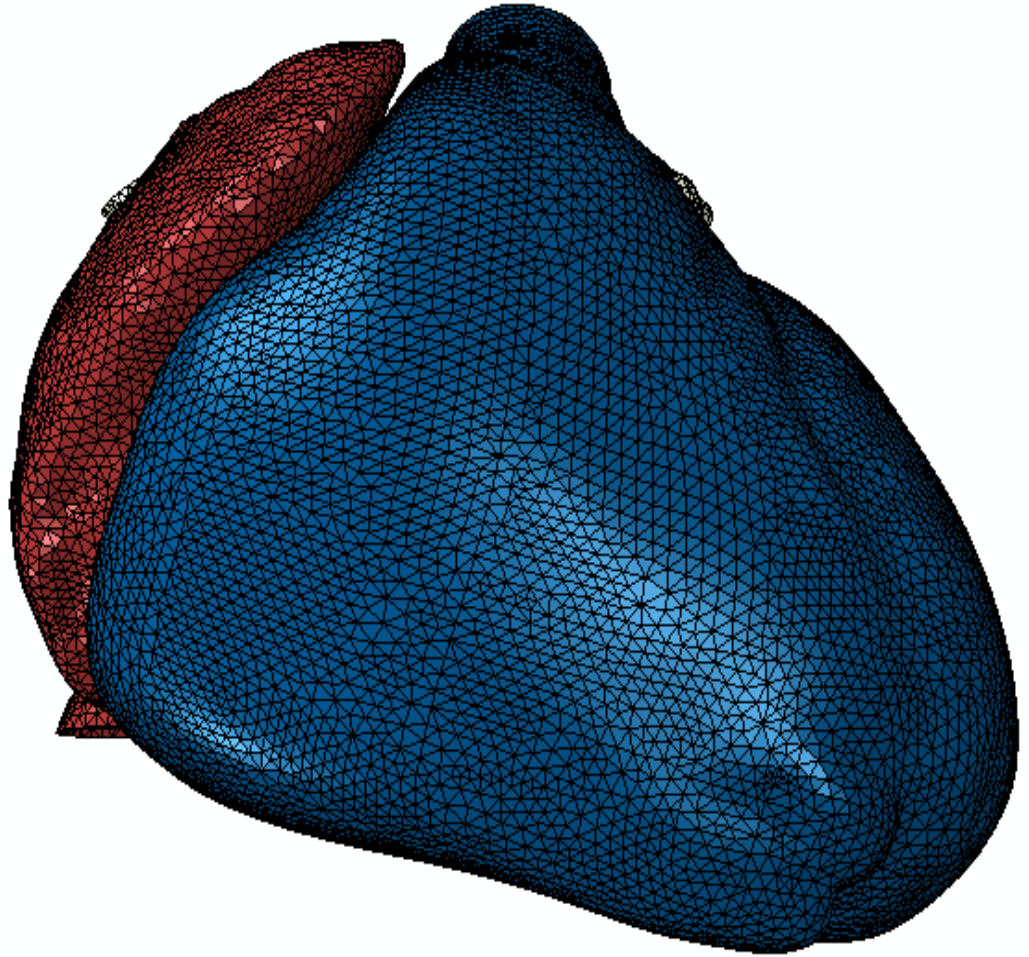
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455 **Figure 1**

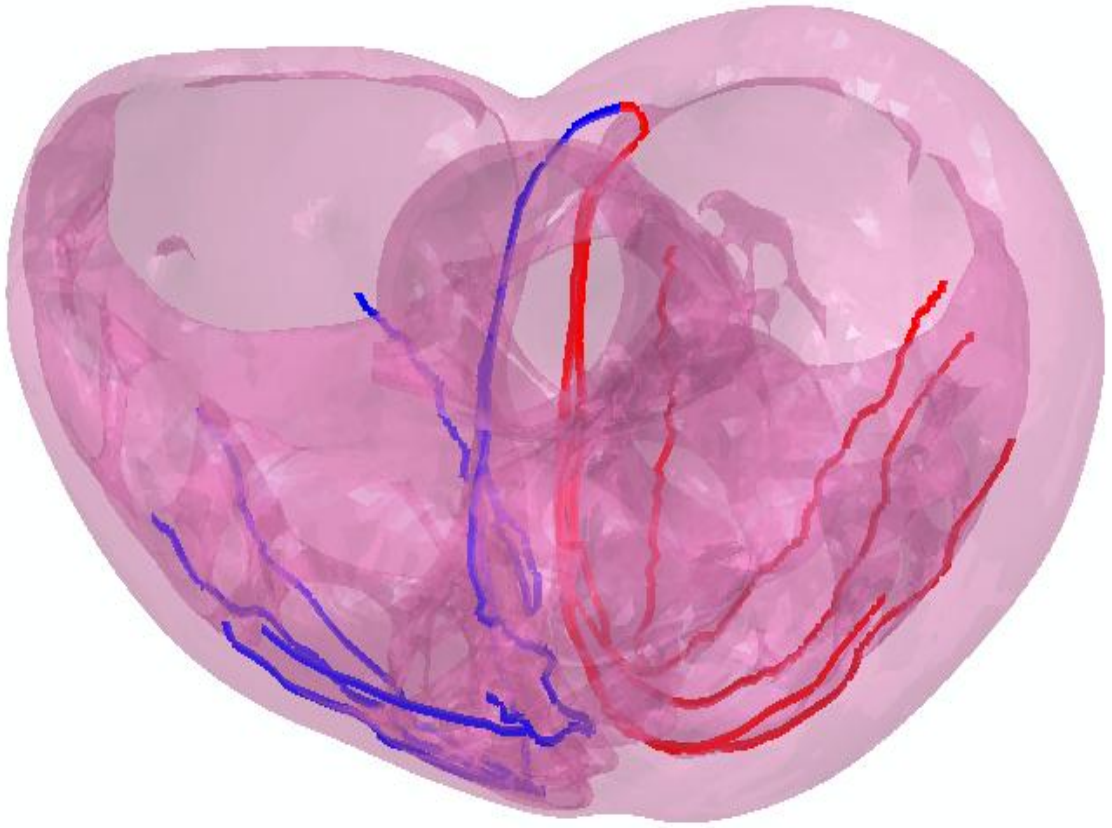
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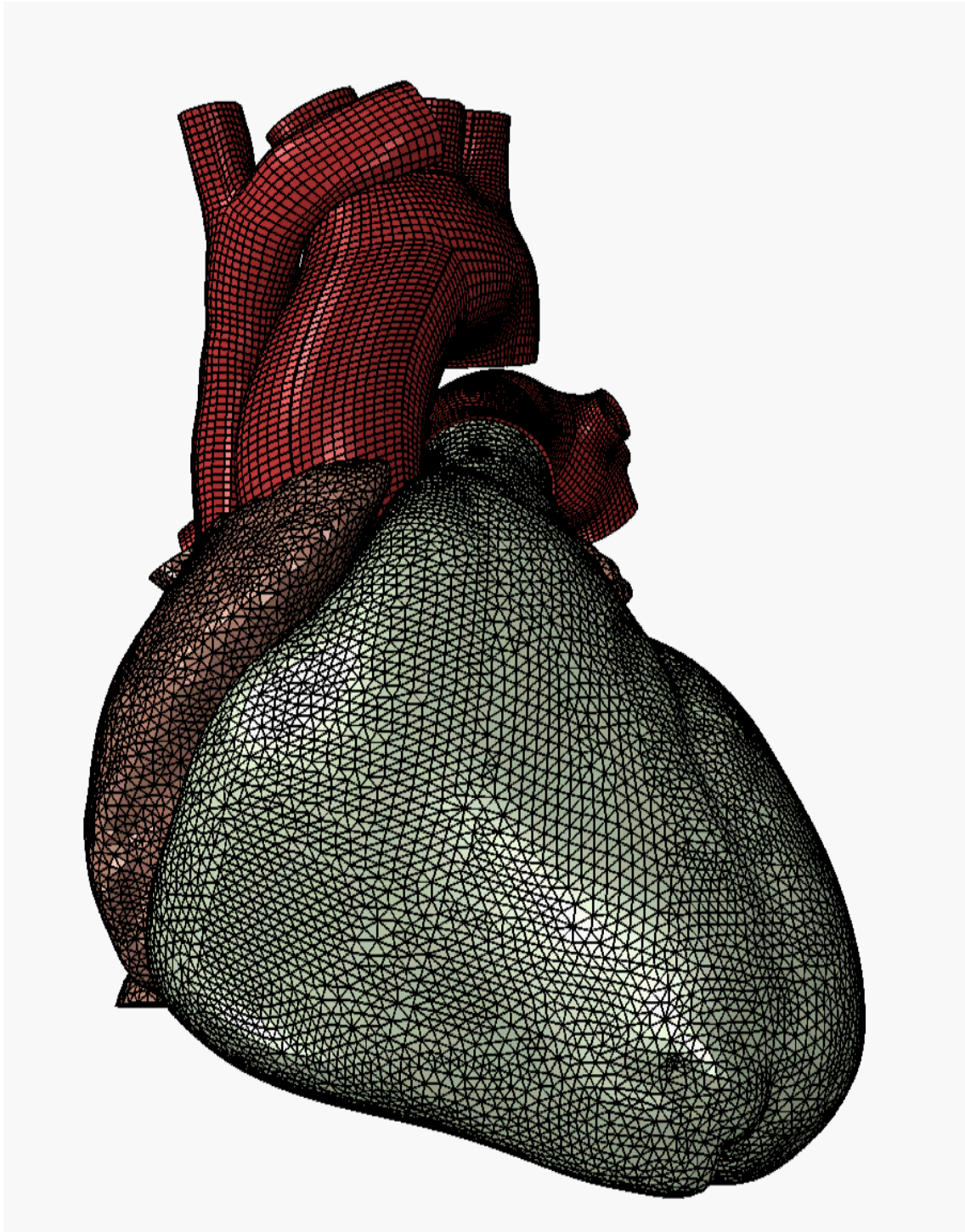
458 **Figure 2**

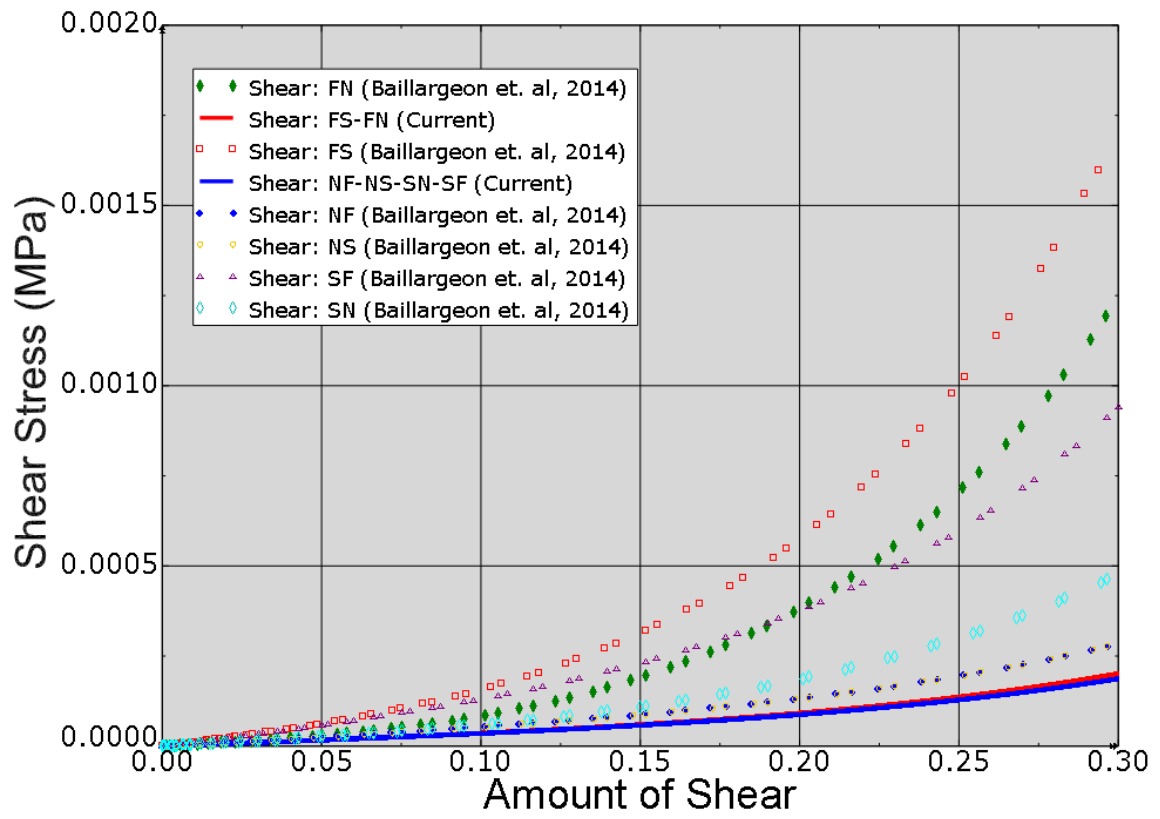
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461 **Figure 3**



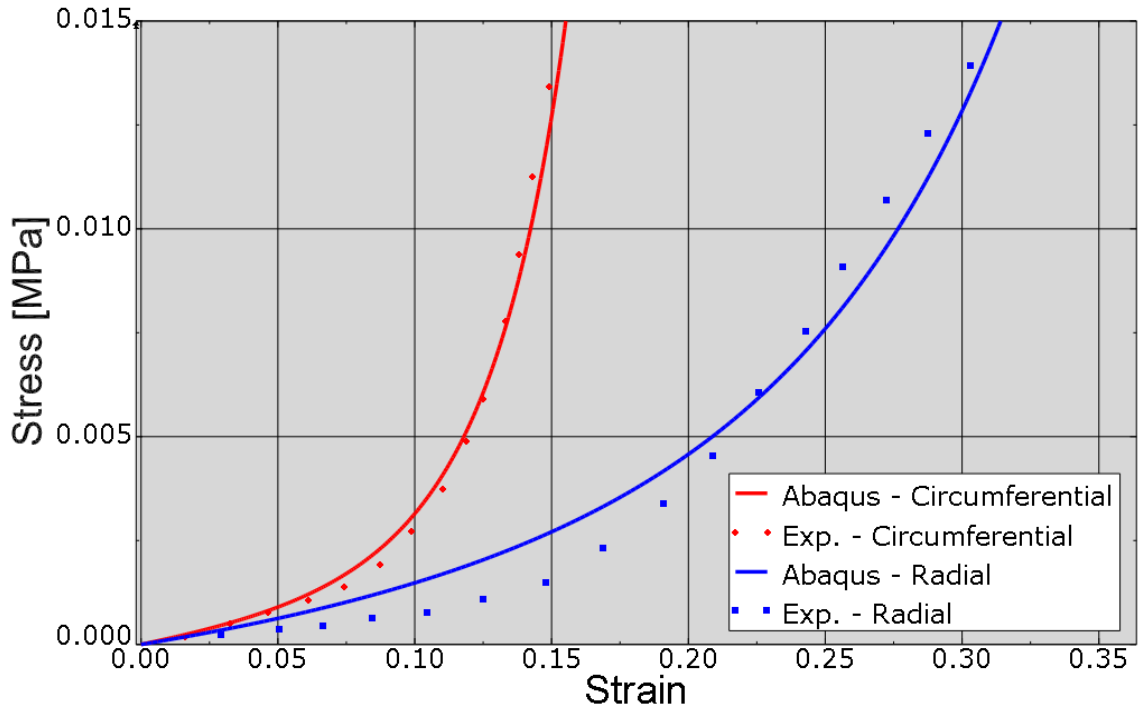


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466 **Figure 5**

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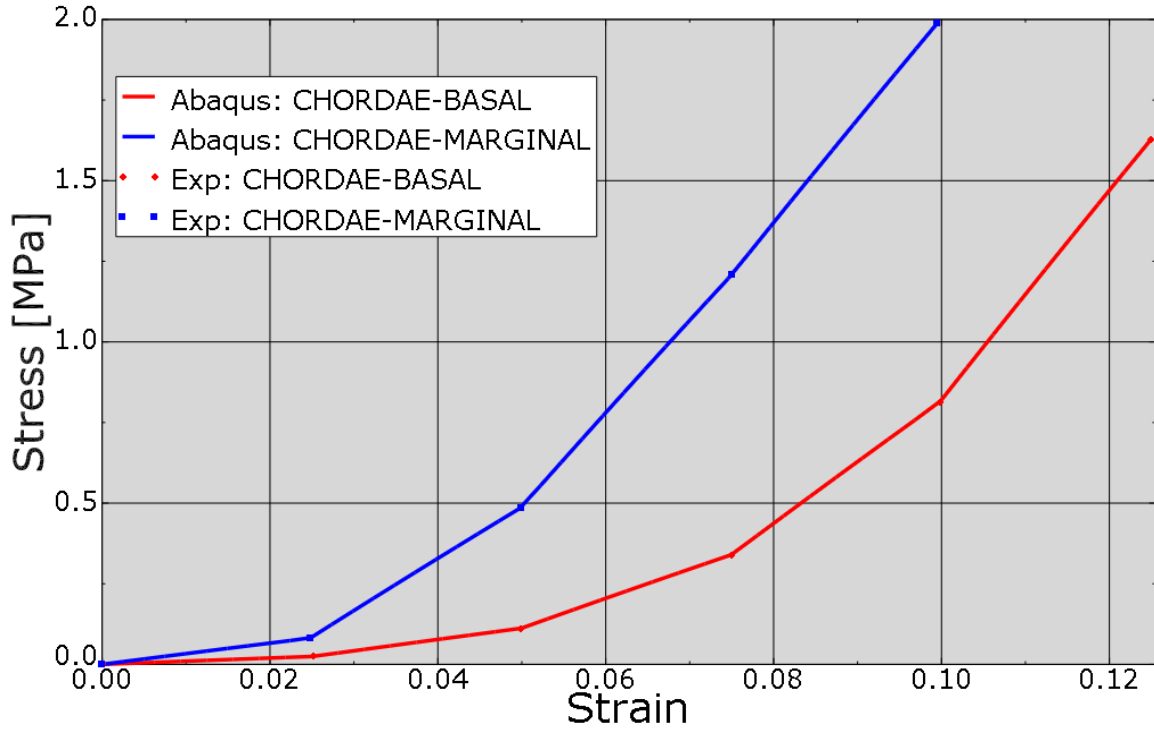


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471 Figure 6

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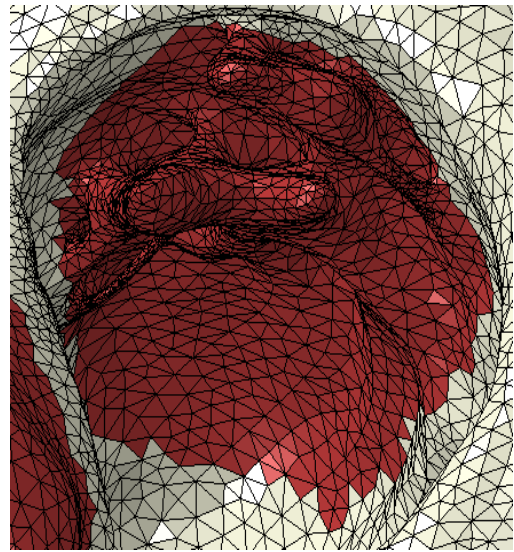
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475 **Figure 7**

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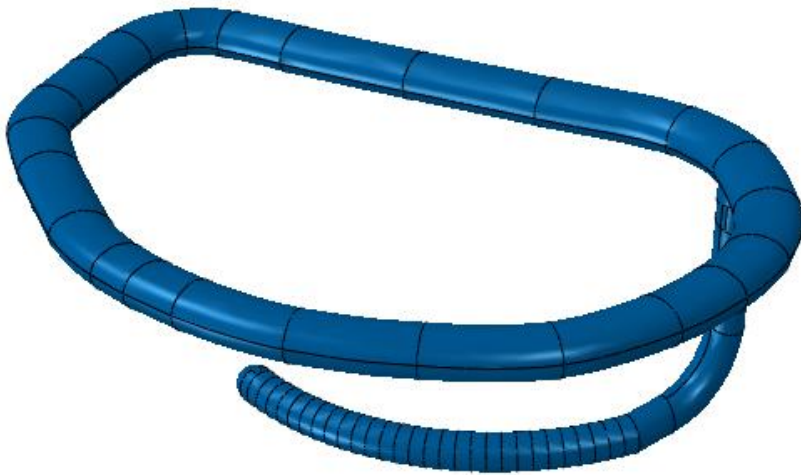
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478 **Figure 8**

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480 **A**

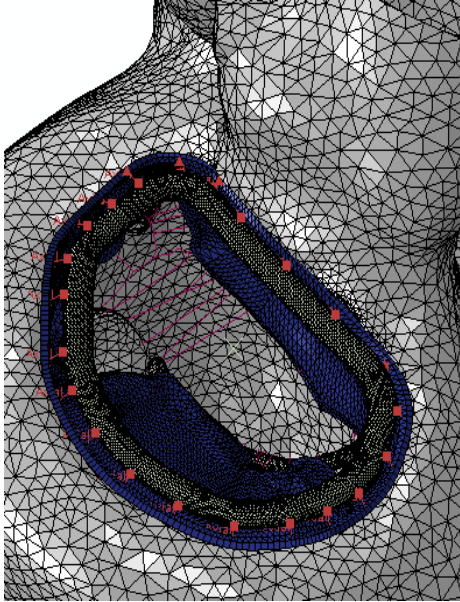


481 **B**

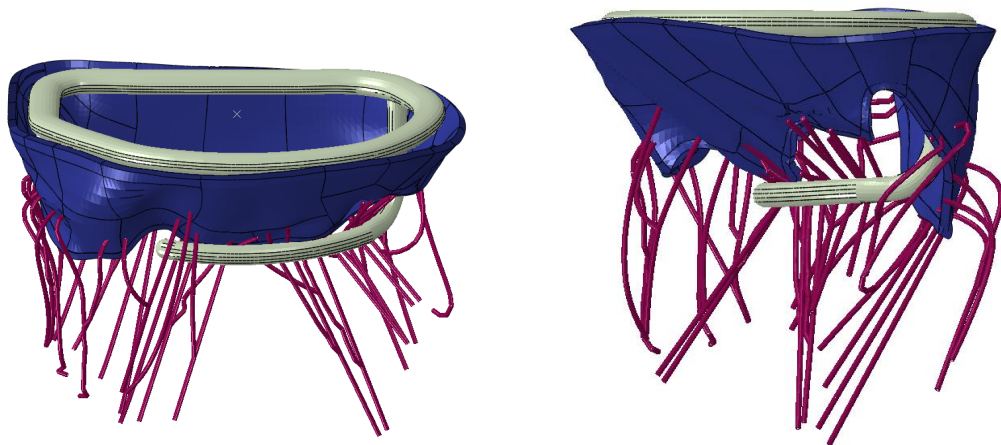
482 **Figure 9**

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485 **A**

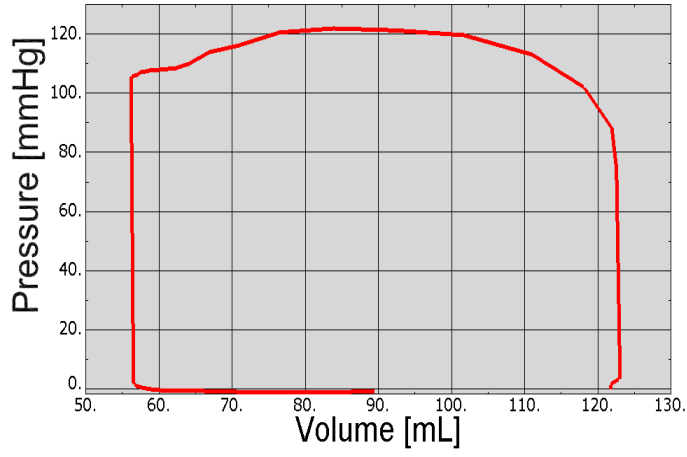


486 **B**

487 **Figure 10**

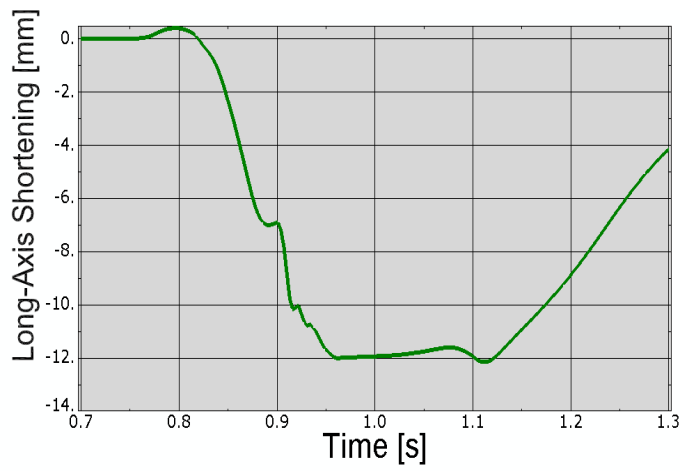
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A



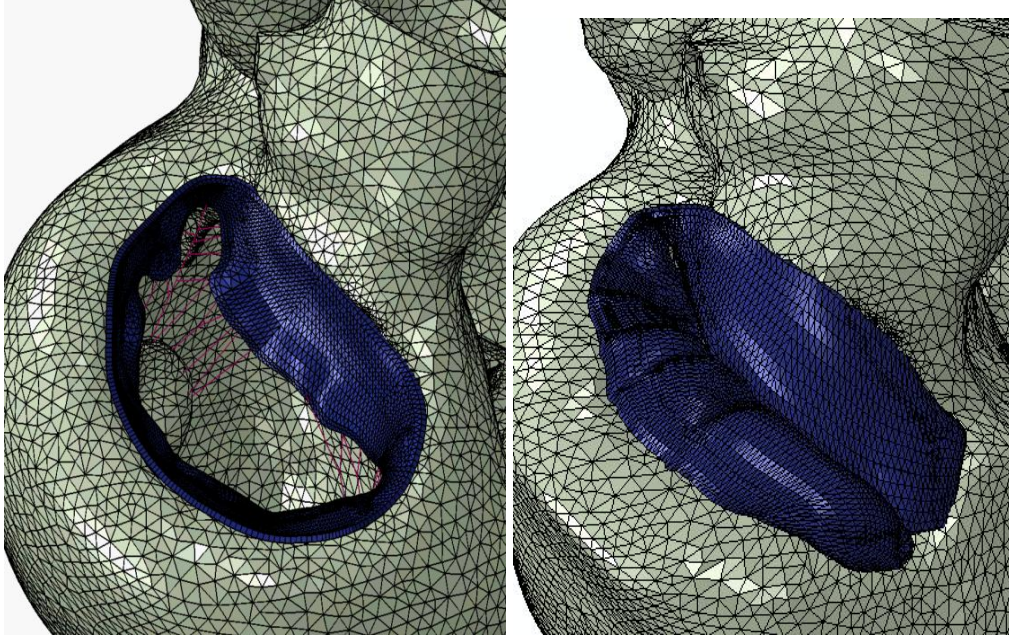
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B

492 **Figure 11**

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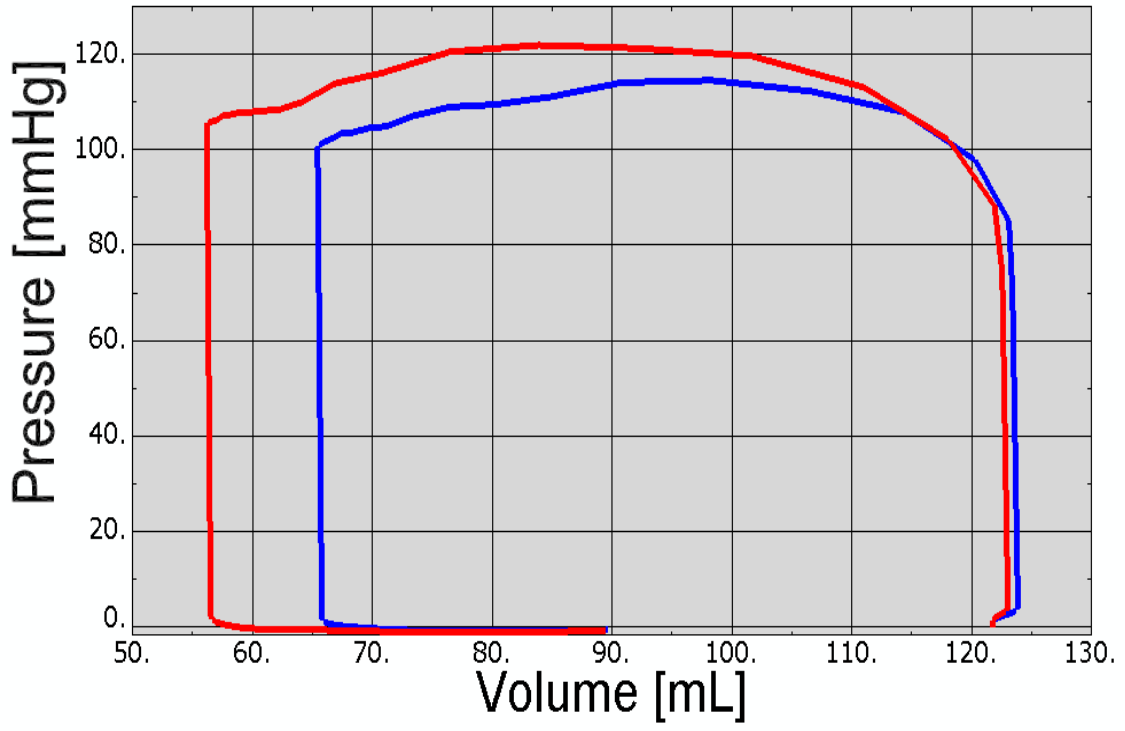


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496 **Figure 12**

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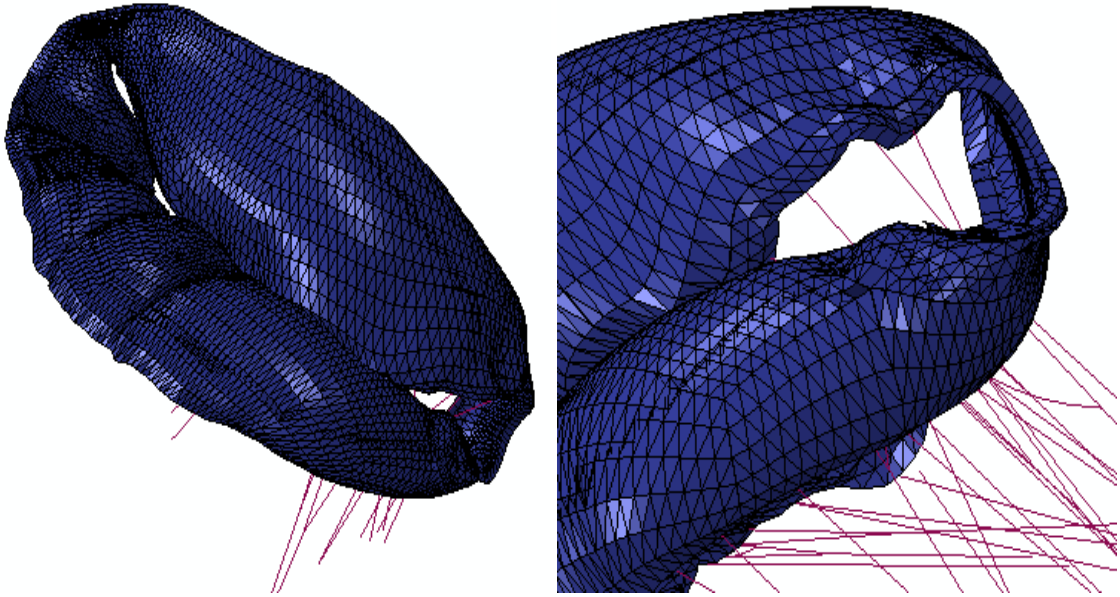


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500 **Figure 13**

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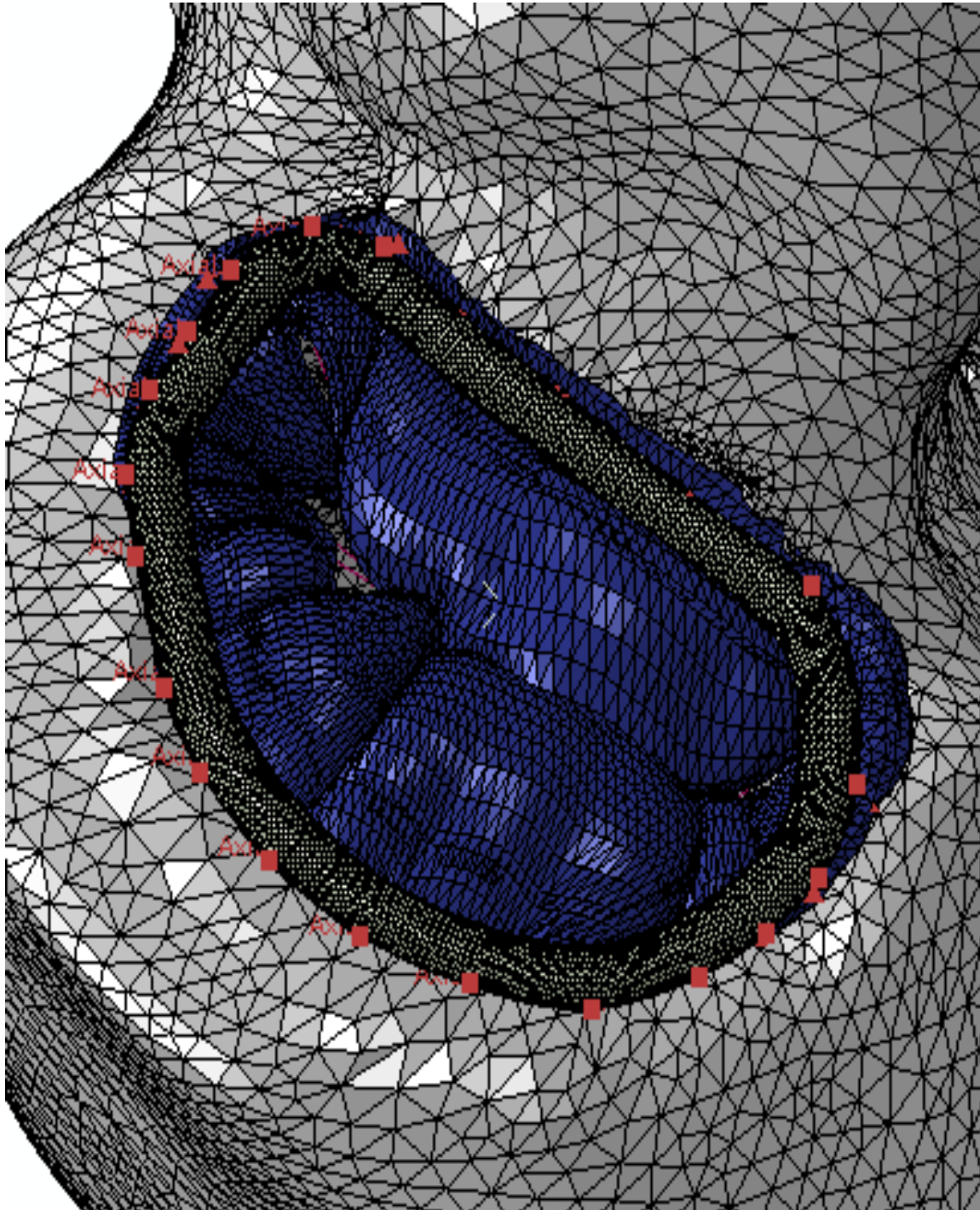
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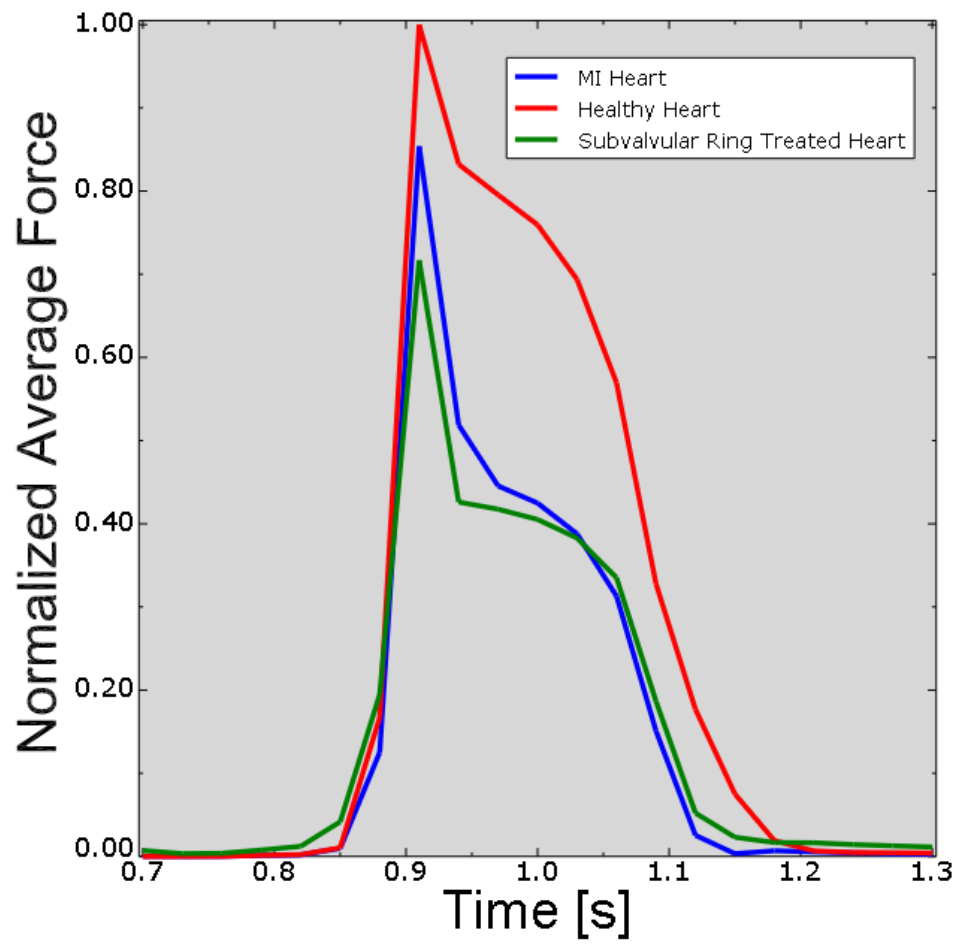


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504 **Figure 14**

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510 **Figure 16**

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