THE EFFECT OF HYDROGEL INJECTION ON CARDIAC FUNCTION IN A POST INFARCTION HEART MODEL

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INTRODUCTION
Cardiovascular diseases (CVD) will become the leading cause of death by 2020. Of all CVD, myocardial infarction has been presented as the most common cause of heart failure [1]. Despite current treatments heart failure is still exceedingly high in patients who survive heart attacks, especially those who suffer large infarcts. The mechanical properties of healing myocardial infarcts are a critical determinant of cardiac pump function and the progression to heart failure [2]. Novel therapies such as modification of the infarcted myocardium are emerging to limit the adverse remodeling of the heart following infarction. It has been shown that polymer injection into the infarct and border zones can improve cardiac function [3]. In this computational study, the effect of hydrogel injection on cardiac function in a large antero-apical (AA) infarct model has been investigated. More specifically, the introduction of multiple thin hydrogel layers into both the ischemic and scarred infarct zones has been examined.

METHODS
The software package, Continuity®6.3b (University of California in San Diego, CA, USA) was used in which a 3D finite element ventricular model is coupled to a lumped parameter systems model of circulation [4]. A pre-existing canine heart model was used including left and right ventricular geometry and a 3D myofiber angle distribution [5]. Passive myocardium (during diastolic filling) was modeled using a nearly incompressible, transversely isotropic strain energy function

\[ W = \frac{1}{2} C (\varepsilon^Q - 1) + C_{\text{compr}} (I_3 \ln I_3 - I_3 + 1) \]

in which

\[ Q = b_f E_{ff}^2 + b_{cc} (E_{cc}^2 + E_{ac}^2 + E_{sc}^2) + b_{fc} (E_{fs}^2 + E_{sf}^2 + E_{fs}^2 + E_{fs}^2) \]

where \( E_{ff} \) is the fibre strain, \( E_{cc} \) is cross-fibre in-plane strain, \( E_{ac} \) is the radial strain transverse to the fibre, \( E_{sc} \) is the shear strain in the transverse plane, and \( E_{fs} \) and \( E_{sf} \) are shear strain in fibre – cross-fibre and fiber – radial coordinate planes, respectively. The diastolic myocardial material parameters; \( C, b_f, b_{cc} \) and \( b_{fc} \) were previously determined for healthy canine myocardium [6]. Active myocardium (during systolic contraction) was modeled as the sum of passive stress derived from the strain energy function, and an active directional component, which is a function of time, peak intracellular calcium concentration, sarcomere length and maximum isometric tension [7].

Figure 1: 3D mesh of the canine heart model; a) healthy model, b) antero-apical (AA) infarct model showing the infarct region (in blue).

Two types of AA myocardial infarct models (Figure 1) were generated. First, an acute ischemic infarct model was created by disabling active contraction in the AA region of the heart. The intracellular calcium concentration in the infarcted tissue was set to zero to shut down active contraction. To simulate the decreasing tissue stiffness over time after myocardial infarction, three versions of this ischemic infarct model were produced. In model 1, the passive mechanical properties of the myocardium were equal to the healthy case while in models 2 and 3 the stiffness \( C \) was only 50% and 25% of the healthy value, respectively. Second, a scarred infarct was modeled as non-contractile and stiff by disabling active contraction and increasing 10-fold the stress scaling coefficient \( C \), respectively [8].

Figure 2: 3D mesh of the canine heart model showing the four alternating thin hydrogel layers (in yellow) incorporated in the AA infarct wall (in blue).
The hydrogel inclusions were described as a structure of four alternating thin layers into the wall of the AA infarct (Figure 2). The total volume of the incorporated hydrogel was equal in all models. Mechanical properties of the hydrogel were defined as isotropic and the stiffness was 50% of the healthy myocardium [unpublished data]. Isotropic material properties were modelled by setting the strain and shear coefficients $b_{in}$, $b_{cc}$ and $b_{bc}$ in the strain energy function equal. Additionally, stiffness was decreased by 50%.

**RESULTS AND DISCUSSION**

To investigate the effect of a particular AA infarct with or without hydrogel incorporation on the cardiac function, pressure-volume (PV) relationships were obtained by using the circulation model. The PV relationships represent the diastolic compliance (passive filling) and systolic elastance (active contraction) of the left ventricle and are shown in Figure 3.

![Figure 3: Pressure (kPa) – volume (ml) relationship for the healthy and different infarct models with and without hydrogel layer inclusion. The curves on the left represent the systolic elastance or contractility and the curves on the right, the diastolic compliance of the left ventricle.](image)

The cardiac functional parameters of the healthy and all infarct models were calculated from the pressure-volume relationships and are shown in Table 1.

In comparison to the healthy case, a decrease in contractility ($E_{max}$) of 32%, 37% and 40% is seen for the infarct ischemic models 1 to 3, respectively. The infarct scar model shows a reduction of 11% in contractility compared with the healthy reference. The decrease in stroke volume (SV) is similar for the three infarct ischemic models and the infarct scar model; 52%, 50%, 48% and 52%, respectively. The ejection fraction (EF) is reduced by 52% for all infarct ischemic models, and by 46% for the infarct scar model, compared to the healthy model.

The incorporation of hydrogel in the AA infarcted wall results in an improvement of cardiac contractility of 14%, 24% and 26%, respectively, for the three infarct ischemic models when compared to the same models without hydrogel inclusion. Additionally, stroke volume values recover by 8%, 4% and 3%, respectively, in the infarct ischemic models and the ejection fraction of the left ventricle rises by 13% for ischemic model 1, 12% for model 2 and 14% for model 3, as a result of the hydrogel layer presence in the heart wall.

No improvement in contractility, stroke volume or ejection fraction is found after hydrogel layer inclusion in the wall of the AA infarct scar model. A positive effect of hydrogel inclusion in scarred myocardium might be observed when a larger amount of hydrogel is injected.

**Table 1:** Cardiac functional parameters contractility ($E_{max}$), stroke volume (SV) and ejection fraction (EF) for the different models.

<table>
<thead>
<tr>
<th>Model</th>
<th>$E_{max}$ (kPa/ml)</th>
<th>SV (ml)</th>
<th>EF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Control</td>
<td>1.158</td>
<td>15.7</td>
<td>0.368</td>
</tr>
<tr>
<td>Infarct Ischemia 1</td>
<td>0.787</td>
<td>7.48</td>
<td>0.175</td>
</tr>
<tr>
<td>Infarct Ischemia 1 + Hydrogel</td>
<td>0.901</td>
<td>8.10</td>
<td>0.197</td>
</tr>
<tr>
<td>Infarct Ischemia 2</td>
<td>0.724</td>
<td>7.82</td>
<td>0.175</td>
</tr>
<tr>
<td>Infarct Ischemia 2 + Hydrogel</td>
<td>0.897</td>
<td>8.12</td>
<td>0.196</td>
</tr>
<tr>
<td>Infarct Ischemia 3</td>
<td>0.693</td>
<td>8.19</td>
<td>0.177</td>
</tr>
<tr>
<td>Infarct Ischemia 3 + Hydrogel</td>
<td>0.876</td>
<td>8.43</td>
<td>0.201</td>
</tr>
<tr>
<td>Infarct Scar</td>
<td>1.030</td>
<td>7.48</td>
<td>0.198</td>
</tr>
<tr>
<td>Infarct Scar + Hydrogel</td>
<td>1.011</td>
<td>7.41</td>
<td>0.195</td>
</tr>
</tbody>
</table>

Mechanical infarct properties affect cardiac performance differently during systole and diastole. A compliant infarct zone impairs systolic ejection or contractility as it is stretched during systole and a stiff infarct region impairs diastolic filling. The improvement of cardiac function due to hydrogel injection is based on a change in mechanical properties of the infarcted wall and has its effect on both phases of the cardiac cycle.

**CONCLUSIONS**

The injection of hydrogel in four thin layers in the AA infarcted ischemic wall has a positive effect on the contractility, stroke volume and ejection fraction of the left ventricle in a canine heart model.

**ACKNOWLEDGEMENTS**

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**REFERENCES**