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A computational pipeline for quantification of mouse myocardial stiffness parameters

Øyvind Nordbø [a], Pablo Lamata [b], Sander Land [b], Steven Niederer [b], Jan M. Aronsen [c,d], William E. Louch [c,e], Ivar Sjaastad [c], Harald Martens [f], Arne B. Gjuvsland [g], Kristin Tøndel [b], Hans Torp [h], Maelene Lohezic [i], Jurgen E. Schneider [h], Espen W. Remme [e,j], Nicolas Smith [b], Stig W. Omholt [k], Jon Olav Vik [g,*]

[a] Department of Mathematical Sciences and Technology, Centre for Integrative Genetics, Norwegian University of Life Sciences, P.O. Box 5003, N-1432 Ås, Norway
[b] Department of Biomedical Engineering, King's College London, St. Thomas' Hospital, Westminster Bridge Road, London SE17EH, UK
[c] Institute for Experimental Medical Research, Oslo University Hospital Ullevål and University of Oslo, Kirkeveien 166, 4th Floor Building 7, 0407 Oslo, Norway
[d] Bjørknes College, Oslo, Norway
[e] KG Jebsen Cardiac Research Center and Center for Heart Failure Research, University of Oslo, 0407 Oslo, Norway
[f] Department of Engineering Cybernetics, Faculty of Information Technology, Mathematics and Electrical Engineering, Norwegian University of Science and Technology, Trondheim, Norway
[g] Department of Animal and Aquacultural Sciences, Centre for Integrative Genetics, Norwegian University of Life Sciences, P.O. Box 5003, N-1432 Ås, Norway
[h] Department of Circulation and Medical Imaging, Faculty of Medicine, Norwegian University of Science and Technology, Postboks 8905, Medisinsk teknisk forskningssenter, NO-7491 Trondheim, Norway
[i] Radcliffe Department of Medicine, Division of Cardiovascular Medicine, University of Oxford, Welcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7BN, UK
[j] Institute for Surgical Research, Oslo University Hospital, Rikshospitalet, Oslo, Norway
[k] Faculty of Medicine, Norwegian University of Science and Technology, P.O. Box 8905, N-7491 Trondheim, Norway

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ABSTRACT

The mouse is an important model for theoretical–experimental cardiac research, and biophysically based whole organ models of the mouse heart are now within reach. However, the passive material properties of mouse myocardium have not been much studied.

We present an experimental setup and associated computational pipeline to quantify these stiffness properties. A mouse heart was excised and the left ventricle experimentally inflated from 0 to 1.44 kPa in eleven steps, and the resulting deformation was estimated by echocardiography and speckle tracking. An in silico counterpart to this experiment was built using finite element methods and data on ventricular tissue microstructure from diffusion tensor MRI. This model assumed a hyperelastic, transversely isotropic material law to describe the force–deformation relationship, and was simulated for many parameter scenarios, covering the relevant range of parameter space. To identify well-fitting parameter scenarios, we compared experimental and simulated outcomes across the whole range of pressures, based partly on gross phenotypes (volume, elastic energy, and short- and long-axis diameter), and partly on node positions in the geometrical mesh. This identified a narrow region of experimentally compatible values of the material parameters. Estimation turned out to be more precise when based on changes in gross phenotypes, compared to the prevailing practice of using displacements of the material points. We conclude that the presented experimental setup and computational pipeline is a viable method that deserves wider application.

1. Introduction

The passive mechanical properties of the heart wall play an important role during the filling of the ventricle; for instance, stiffening of the myocardium can lead to diastolic dysfunction and heart failure [1]. Incorporating patient-specific geometries and

Abbreviations: LVP, Left Ventricular Pressure; MVO, Mitral Valve Opening; ED, End Diastole; ES, End Systole; PV, Pressure Volume

* Corresponding author. Tel.: +47 45882998; fax: +47 64965101.
E-mail address: jonovik@gmail.com (J.O. Vik).

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material properties into biomechanical models holds promise for the improved diagnosis and treatment of heart failure [2,3]. In biomechanical models, the stress–strain relationship for myocardial tissue is described by constitutive laws whose parameters describe the material stiffness along the microstructural axes, e.g. fibre and sheet directions. Several studies have quantified passive myocardial stiffness in humans [3–5] and model organisms, such as the pig [6,7], dog [8,9], and rat [10] (see Table 1, with references). Less well studied, however, is the mouse, which is an important model organism in cardiac research. Transgenic mouse models have been extensively used in cardiac research over the last decade, where manipulation of the mouse genome has provided several novel insights in the development of cardiac disease [11]. Alterations of the myocardial properties of the heart, both in the extracellular matrix and in the cardiomyocytes, are suggested to play a major role in development of diastolic dysfunction and heart failure. Several mutations leading to heritable heart disease occur in both mouse and human [11], and the hearts have similar composition and function with regards to mechanical properties [12].

Here we propose a workflow for estimation of passive material properties of mouse myocardium by comparing computer simulations of soft tissue mechanics to observed deformation under passive inflation of an excised mouse heart. Firstly, we estimate trajectories of material points by speckle tracking of echo data through the deformation from zero to end diastolic pressure levels. This deformation is used, together with fibre structure obtained from diffusion tensor MRI, to build meshes for computer simulations. Secondly, we run model simulations and use full factorial experimental designs to cover the biological relevant region of the parameter space for the transversely isotropic Guccione law [13]. The results show that the parameters of the constitutive law are not separately identifiable from these passive inflation measurements alone, in accordance with previous studies [14–16]. For the four-dimensional parameter space of the material law, we identify an elongated region of parameter combinations with nearly equivalent good fit to deformation data from passive inflation. We describe the structure of this parameter redundancy, and compare our findings with published estimates. Following a discussion of its advantages and limitations, we conclude that the presented pipeline merits wider application.

2. Methods

The quantification of the passive mechanical properties of the myocardium relies on mechanistic models whose parameters are tuned to reproduce the observation of a corresponding experiment [9,14,15]. Below we describe the passive inflation experiment with deformation measurement, MR imaging for geometric meshing, image processing and speckle tracking to estimate deformation, mechanics simulations, and comparison of experiment and simulation.

2.1. Passive inflation experiment

A single mouse was anesthetized with 5% isoflurane and sacrificed by cervical dislocation. The heart was then rapidly excised and cannulated via the aorta and mounted on a Langendorff setup (Fig. 1). The cannula was firstly placed over the level of the aortic valves, to perfuse the myocardium with cardioplegic solution of pH 7.4, 118.3 mM NaCl, 3.0 mM KCl, 4 mM $MgSO_4$, 0.2 mM $CaCl_2$, 2.4 mM KH_2PO_4, 24.9 mM $NaHCO_3$, 10 mM glucose, 2.2 mM mannitol. Some calcium was included in the superfusate since calcium-free conditions promote breakdown of gap junctions and dissociation of cardiomyocytes [17], which could cause underestimates of myocardial stiffness. The cannula was then introduced into the left ventricle, and thereafter retracted into the aorta. This technique allowed the cannula both to manipulate left ventricular pressure and to perfuse the coronary arteries; the latter was found necessary to prevent ischemia and stiffening in preliminary experiments. Pressure was increased from 0 kPa to approximately 1.44 kPa over 10 s by adjusting the height of a fluid column connected to the cannula. Deformation of the left ventricle

Table 1
Studies estimating the parameters in the Guccione and Costa material laws. For the current study, parentheses show the range of each parameter among scenarios that fit within a 25% increase from the minimum value of the objective function (i.e. least lack-of-fit). The Costa law is a generalization of the Guccione law, with separate coefficients for each term in the parentheses in Eq. (5). See Supplementary Fig. S1 for a visualization of the stress–strain relationships corresponding to these parameter scenarios. ED=End Diastole, ES=End Systole, PV=Pressure Volume, MVO=Mitral Valve Opening

Study	Experiment	Reference configuration	Recording	Time-points used	Species	a (kPa)	b_1	b_2	b_3
Guccione law									
[10][a]	Passive inflation	Cylinder	PV-curves, implanted markers	5	Rat	2.2	9.2	2.0	3.7
					Dog	2.4	26.7	2.0	14.7
[8]	Epicardial suction	Zero pressure	Tagged MRI	3	Dog	0.10–1.0	39.5–93.0	6.1–61.6	3.1–73.1
[14]	Passive inflation	Zero pressure	Tagged MRI	5	Pig	3.0	11.1	1.8	10.0
[41]	In vivo	MVO	Tagged MRI	2 (ED, ES)	Sheep	0.12–0.35	9.2–67.1	5.0–26.6	9.3–21.6
[6]	Passive inflation	Low pressure	Tagged MRI	5	Pig	0.07–0.79	8.0–83.4	6.1–36.4	8.2–62.4
[44]	In Vivo	MVO	Tagged MRI	2 (ED, ES)	Sheep	0.95	49.3	19.2	17.4
[9][a]	In Vivo	MVO	Tagged MRI, pressure wire	2 (MVO, ED)	Dog	1.7	14.3	4.5	0.76
[24]	In Vivo	Zero pressure	Tagged MRI, pressure wire	2	Human	0.3	41.7	9.1	51.5
[45]	Passive inflation	Mid Diastole	PV-curves	3	Mouse	1.1	8.0	2.0	3.7
[15][a]	In vivo	Calculated	Tagged MRI, pressure wire	4–6	Human	2	19.3	10.7	12.8
Costa law[b]									
[46][a]	In vivo	Ellipsoid	Implanted markers	2 (ED, ES)	Dog	1.8	6.0	3.0–12.0	3.0–7.0
[47]	Shear tests	Unstressed	Tissue block	Several	Pig	0.22	42.5	7.8–18.6	10.9–11.0
[7]	Shear tests	Unstressed	Tissue block	Several	Pig	0.26	37.2	9.1–18.9	12.0
[48]	Passive inflation	Calculated	PV-curves	Several	Human	0.3	39.0	4.2–7.6	12.8–17.2
Current study	Passive inflation	Zero pressure	Echocardiography	8	Mouse	3.1 (2.0–5.6)	5.0 (2.7–7.0)	3.7 (2.1–5.2)	2.6 (1.5–6.0)

[a] These studies used a definition of a that was twice the one used in the other studies. Estimates in this table have been halved to make them directly comparable with the others.

[b] The orthotropic Costa law has three parameters in place of b_2 and two in place of b_3. The values in the b_2 and b_3 columns for Costa-law studies show the variability between these non-isotropic coefficients.