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Appendix E1

Investigating cTSD and Wall Thickness in HCMNet

Motivation

The primary result of this work is that the quantity cTSD, which we define as the difference between epicardial and endocardial circumferential shortening, is higher in subjects with preclinical HCM compared with control subjects. Although wall thickness was similar between the two groups, we wanted to thoroughly examine the possibility that the higher cTSD could be the result of mild, statistically insignificant thickening.

By treating the myocardium in short axis as two concentric circles, we can predict cTSD entirely in terms of outer end diastolic radius ($\varepsilon_{rout,ed}$), end diastolic wall thickness (wt_{ed}), epicardial strain (ε_{epi}), and a chosen increase in myocardial area (A_{exp}). Here, we compare our measured cTSD values with those predicted by this cylindrical model when A_{exp} is set empirically to biologically plausible values. We show that cTSD values predicted by this model follow a similar trend to those which we measured experimentally, but that the control and preclinical groups are statistically different only in terms of measured cTSD, not predicted cTSD.

Proof

We define cTSD in terms of endocardial and epicardial circumferential shortening:

$$\mathrm{cTSD} = \varepsilon_{epi} - \varepsilon_{end}\,.$$

Treating the myocardium in short axis as two concentric circles, we can rewrite cTSD in terms of inner and outer radii at end diastole and end systole:

$$\mathrm{cTSD} = \frac{(r_{out,es} - r_{out,ed})}{r_{out,ed}} - \frac{(r_{in,es} - r_{in,ed})}{r_{in,ed}}\,.$$

Additionally, we make the assumption that the area of the myocardium increases by a constant factor A_{exp}:

$$0 = A_{exp}(r_{out,ed}^2 - r_{in,ed}^2) - (r_{out,es}^2 - r_{in,es}^2)\,,$$

and solve this equation for $r_{in,es}$:

$$r_{in,es} = \pm\sqrt{A_{exp}\left(r_{in,ed}^2 - r_{out,ed}^2\right) + r_{out,es}^2}\,.$$

Taking the positive square root of $r_{in,es}$ and writing $r_{out,es}$ and $r_{in,ed}$ in terms of known quantities, we may write cTSD in terms of epicardial strain (ε_{epi}), the outer radius at end diastole ($r_{out,ed}$), and end diastolic wall thickness (wt_{ed}) cTSD =

$$\varepsilon_{epi} - \frac{-r_{out,ed} + wt_{ed} + \sqrt{A_{exp}\left(\left(r_{out,ed} - wt_{ed}\right)^2 - r_{out,ed}^2\right) + \left(r_{out,ed}\varepsilon_{epi} + r_{out,ed}\right)^2}}{r_{out,ed} - wt_{ed}}.$$

Results

Across all segments and slices, Moore et al (9) report in the text that endocardial and epicardial circumferential strain are 32 ± 4% and 16 ± 4%, or cTSD of ≈ 16%. In our control subjects, we report cTSD of 13.6%. To perform the simulation, we set Aexp so as to match the mean predicted cTSD in the control group to Moore's and our own measured values (Aexp = 1.23 and Aexp = 1.17, respectively).

Our measured cTSD values, and predicted cTSD values at the two area factors are shown in Figure E2. The measured and predicted cTSD values appear to be broadly correlated. This suggests that our model is reflective of biologic contraction, and accounts for some fraction of the observed difference. Moreover, our measured values show that the preclinical group is intermediate between the control and overt groups, and the preclinical group has significantly higher cTSD compared with the control group. Though some difference between control and preclinical values is noted in the simulations, the results do not reach statistical significance. This suggests that some amount of the observed difference in cTSD may be due to mild wall thickening, but equally that there is an additional mechanism independent of simple geometric considerations.