Effects of Diastolic Properties During Remodeling in Heart Failure

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Introduction: Although the physiological states of hypertrophic remodeling and congestive heart failure have been intensively studied, little is known about the transition from one to the other. Previous studies have implicated diastolic dysfunction as a possible mechanism of failure[1]. The availability of gene-targeted mouse models has reinforced the significance of high field murine cardiac imaging in characterizing the progression of remodeling and its ultimate decompensation to failure. Mice that are homozygous null for muscle LIM-domain protein (MLP) exhibit clinical characteristics of human dilated cardiomyopathy, with systolic function depressed after two weeks of age, and continued progression towards congestive heart failure[2]. In this longitudinal study, MR imaging was used in conjunction with invasive catheter techniques to investigate the time course of remodeling. The novel integration of both experimental approaches with finite element analysis was used to estimate the end diastolic pressure volume relationship (EDPVR) and conclude the relative balance between factors determining its shape. The hypothesis is thus that the relative effects of diastolic properties, in particular those of geometry and global compliance, effect ventricular function during hypertrophic remodeling and may influence the eventual decompensatory transition towards congestive heart failure.

Methods: Five MLP$^{(-/-)}$ and four non-failing wildtype controls (129/Sv) were imaged weekly from 2-3 to 32 weeks of age. *In vivo* NMR murine cardiac imaging was performed on a 7T horizontal-bore Varian MR scanner, equipped with a shielded 12 cm bore Magnex gradient system (22 G/cm, risetime 300 μs), and a custom designed 19 mm quadrature driven TEM coil. High resolution MR experiments were conducted using an ECG and respiratory triggered FLASH Gradient Echo (GE) pulse sequence (α=90°, TE=1.8ms, TR~R-R interval, 5 avgs) employing fractional echo and time series averaging. Continuous and simultaneous pressure and volume measurements were invasively obtained directly from the left ventricular cavity using a 1.4F conductance catheter (Millar Instruments) in forty MLP$^{(-/-)}$ and forty six 129/Sv mice. Hemodynamic data was calibrated and analyzed to yield parameters such as ejection fraction (EF), end-diastolic pressure (EDP) and end-diastolic volume (EDV). Computational finite element techniques incorporated geometric data from MR images with hemodynamic data in an optimization scheme to fit the EDPVR at weeks 15 and 31, which precede and follow an abrupt phase of anatomical remodeling.

Results: Figure 1 illustrates the time course for a dilatation index, defined as the ratio of LV chamber volume to LV epicardial volume, which serves as a three-dimensional analog of a radius to wall thickness ratio. Of particular note is the abrupt onset of dilatation. Prior to about 18 weeks of age, MLP$^{(-/-)}$ hearts have geometrical ratios comparable to wildtypes, but progress through a rapid phase of dilatation in the following 8-9 weeks to plateau again near week 27. This accelerated rate of remodeling was reproducible throughout the sample group and marks a clear transition in anatomical structure. In addition, systolic function was seen to improve temporally concurrent with this dilatation phase, as evidenced by an increase in both stroke volume (SV) and EF (data not shown). Hemodynamic experiments verified the improvement in SV and EF, and also showed EDP to decrease while EDV increased from 15 to 31 weeks of age. Data from both MR and catheter studies were used in a finite element model to estimate the EDPVRs shown in Figure 2. Although possessing a stiffer myocardium as reflected in a leftward shifted stress-strain curve (data not shown), MLP$^{(-/-)}$ hearts at 31 weeks are more compliant versus both younger knockouts and controls at either time point. The fit points represent working pressures of the heart on that curve.

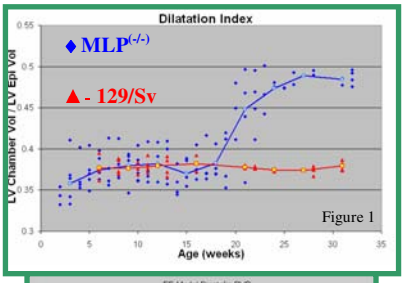

Figure 1

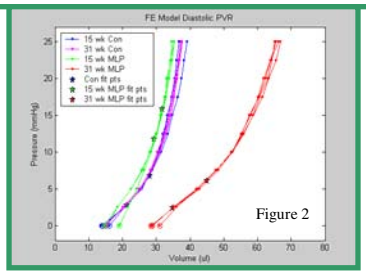

Figure 2

Discussion: The improvement in systolic performance, although temporally concurrent with a classically maladaptive phenomenon such as dilatation, appears evident in terms of the parameters measured in this study, yet its origins remain unclear. Although theories on the transition towards failure as a process are difficult to formulate, one may speculate based on results for this model. At 15 weeks the EDPVR in the MLP$^{(-/-)}$ is comparable to controls. The slightly stiffer curve may be a function of the increased myocardial stiffness and the lack of any dilatation. At that time, EDP in the MLP$^{(-/-)}$ is elevated suggesting that, in the continued absence of geometrical change via dilatation, function is being maintained by the Frank-Starling mechanism where working pressures are higher up on the EDPVR curve. As the pressures continue to rise a physiological limit will be reached where dV/dP approaches zero. A phase of dilatation may ensue to serve multiple purposes. First, global compliance of the ventricle will increase aiding in filling. Second, working pressures will decrease back towards normal levels restoring the ability to again operate on increasing portions of the Frank-Starling curve. Mediated by changes in diastolic properties, there may exist a balance between utilizing the Frank-Starling mechanism and structural remodeling that allow for sustained or even improved systolic performance. A limit to this compensatory mechanism may be reached that marks the threshold to overt failure. From the integration of serial MR imaging and invasive surgical techniques with computational methods in a clinically relevant cardiovascular model, an understanding may be gained of the progression of hypertrophic remodeling and its transition towards overt congestive heart failure.

References:
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2. Arber, S. (1997) *Cell*; 88(3):393-403.