Abstract

Purpose of Study: Heart failure (HF) impacts patients of all ages and is an enormous public health problem. Historically, HF has been treated with a single, multi-purpose approach, despite the observation that biological differences such as age influence the pathogenesis and thus treatment of the disease. We hypothesized that molecular mechanisms of HF pathogenesis differ across the life-course, a hypothesis which we tested with a mouse model of cardiac dysfunction at three distinct stages of life.

Methods Used: C57BL/6 mice at pediatric (5 weeks; n=12), adult (5 months; n=12), and old (18 months; n=12) ages were treated with a subcutaneous mini-osmotic pump that released isoproterenol (ISO) at varying concentrations. RNA sequencing identified that 119, 1515, and 33 genes were significantly differentially expressed in pediatric, adult, and old mice exposed to ISO, respectively (p<0.05). Of these genes, only 2 transcripts were non-selective β-adrenergic receptor agonist commonly used to induce acute cardiac hypertrophy in mice. Following 6 days, we performed echocardiography, biochemical assessments, and RNA sequencing at the left ventricle (LV).

Summary of Results: Both the pediatric and adult groups underwent hypertrophic remodeling in response to ISO, as evident by higher LV weight relative to tibia length (TL). However, ISO exposure did not increase LV/LTL in old mice. RNA imaging demonstrated thickening of the ventricular wall in ISO mice compared to control. Expression of pro-fibrotic mediators also differed across the life-course in response to ISO, with adults inducing a pro-fibrotic transcriptional program (smooth muscle actin, fibronectin, collagen, periostin) that was attenuated in old and absent in pediatric animals. RNA sequencing identified that 119, 1515, and 33 genes were significantly differentially expressed in pediatric, adult, and old mice exposed to ISO, respectively (p<0.05). Of these genes, only 2 transcripts were differentially expressed across all three ages.

Conclusions: Biological age significantly impacts the molecular mechanisms of ISO-induced cardiac remodeling. Ongoing analysis of these molecular targets will inform HF therapies using age as a biological variable.

Background

Pediatric

Adult

Old

Figure 1: Age-specific changes in heart remodeling

Figure 2: (A)SEM of pediatric and adult cardiac sarcomeres. (B) Quantification of sarcomere thickness

Figure 3: Identification of juvenile protective factors to rejuvenate the aging heart

Figure 4: Differences in heart failure based on age in patient

Figure 5: Echocardiography analysis of heart function viewed from the parasternal short axis in M mode

Figure 6: Left ventricular weight relative to tibia length

Figure 7: Results of preliminary RNA sequencing demonstrating number of genes expressed in different ages of mice exposed to ISO

Methods and Experimental Design

Molecular changes: Hypertrophy, Fibrosis, Gene expression

Pathway analysis for targeted therapeutic intervention

Summary of Results:

- Pediatric and adult mice underwent hypertrophic remodeling in response to isoproterenol, whereas old mice did not.
- Echocardiography data demonstrated thickening of ventricular wall in ISO mice compared to control.
- Pro-fibrotic genetic expression differed between age groups in response to isoproterenol.

Ongoing Questions:

- How does sex, in addition to age, affect cardiac remodeling?
- Can we utilize the differences in the pro-fibrotic gene expression due to age and sex to inform new heart failure therapies?

Acknowledgements

The authors thank: University of Wyoming College of Health Science Faculty Aid; Institutional Development Award (IDeA) from NIGMS/ NIH #2P20GM103432; University of Washington School of Medicine WWAMI Program–Laramie Foundation Site

Table 1: Summary of Morphometric Means for Mice Cohort

Table 2: Changes in pro-fibrotic gene expression based on age

Table 3: Summary of echocardiography data means