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From pediatrics to geriatrics: mechanisms of heart failure across the life-course

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Abstract

Heart failure (HF) is a significant public health problem and a disease with high 5-year mortality. Although age is the primary risk factor for development of HF, it is a disease which impacts patients of all ages. Historically, HF has been studied as a one-size fits all strategy- with the majority of both clinical and basic science investigations employing adult male subjects or adult male pre-clinical animal models. We postulate that inclusion of biological variables in HF studies is necessary to improve our understanding of mechanisms of HF and improve outcomes. In this review, we will discuss age-specific differences in HF patients, particularly focusing on the pediatric and geriatric age groups. In addition, we will also discuss the biological variable of sex. Characterizing and understanding the mechanistic differences in these distinct HF populations can provide insights that will benefit and personalize therapeutic interventions. Further, we propose that future investigations into the cellular mechanisms involved in the developing and juvenile heart may provide valuable insights for targets that would be beneficial in aging patients.

1. Introduction

Despite concerted scientific and clinical efforts, heart failure (HF) remains an enormous public health problem with no improvement in 5-year survival since 1998 [1]. HF is a heterogeneous disease, and as such, recent efforts have turned to personalized medicine to improve HF therapy [2]. These efforts are largely based on the observation that the genotype of patients with HF, such as common genetic variants of β -adrenergic or endothelin receptors, alters the response to HF therapy. Similarly, HF phenotype-based personalized medicine has also emerged as a strategy to more effectively treat patients with HF with preserved ejection fraction (HFpEF), a significant public health concern in the aging population [3]. Another component of a personalized approach to HF therapy is the impact of age on HF phenotype. In this review, we will summarize what is known about HF epidemiology, pathophysiology, and therapeutic outcomes in two distinct populations (pediatric and geriatric), and propose that personalized approaches must consider age as a

biological variable. Specifically, we will discuss hypertrophy, fibrosis, and inflammation as central HF mechanisms which differ in pediatric, adult, and aged patients. Further, we propose that by understanding age as a biological variable, it may be possible to improve HF therapy for all populations.

Before we can rigorously discuss age as a biological variable and design therapies targeted at pediatric, adult, or aged populations, it is necessary to first define these terms. Though to some extent, these lines are drawn arbitrarily, they do serve to define cut-offs in both the preclinical and clinical literature. According the Food and Drug Administration, patients from birth to 18 years of age fall within the classification of pediatric. Therefore, in general, most of the studies characterizing pediatric HF consider pediatric patients to be patients less than 18 years of age [4–7]. However, functional differences exist in the adolescent (post-puberty) patient population, specifically sex-differences [8]. The Center for Disease Control and World Health Organization define aged populations as 65 chronological years in human studies, with further classification of the oldest old >80 years. By definition, adults are identified as individuals from 18–65, an incredibly large and diverse age-range.

In an attempt to study young and aged populations pre-clinically, scientists have historically calculated laboratory animal lifespan and extrapolated how rodent ages align on the human age spectrum. For example, laboratory mice have a maximum lifespan of roughly 3 years, and are considered “pediatric” before sexual maturity (roughly 6 weeks of age), or aged at 18 months old. Rats, which have a maximum lifespan of closer to 4 years, are generally considered pediatric before sexual maturity (roughly 6 weeks of age) and aged at ~24 months. In the case of laboratory models, there are several limitations in studying these age groups. Very young animals are still not weaned and differences in maternal diet also play an important role in heart function [9]. Very old mice and rats are more prone to underlying age-associated diseases (i.e. cancer, diabetes, cardiovascular disease) and are generally poor research models [10]. Natural attrition at 30 months of age in mice (~80% max lifespan) and 36 months rats is close to 75% (NIA Strain Survival Information), making manipulation of mechanistic pathways and interventions difficult. In addition, it is important to note that maximum lifespan varies greatly depending on strain, size, as well as environmental influence such as dietary composition. Therefore, it is important to take into account strain-specific variations [10]. Further complicating the definition of age is the notion of using “biological age” instead of “chronological age,” taking into account factors such as frailty and comorbidities [11]. Despite the lack of a clear cut-off for “geriatric” or “pediatric”, it is evident the population’s youngest and oldest cohorts are distinctly different with regard to cardiac physiology and pathophysiology and discussion of these important differences will be the focus of this review.

2. The pediatric heart and postnatal development

Developmental changes in the heart and cardiomyocytes during fetal development are well described in the literature. However, development differences do not end at birth, as cardiomyocytes in the postnatal heart employ cellular mechanisms that are unique from both fetal and adult hearts due to distinct circulatory, respiratory, and energy demands at different developmental stages. During fetal development, the heart pumps blood in a low-pressure

system and the right and left ventricular pressures are the same [12]. Fetal energy utilization is also unique from adults, with fetal myocytes drawing the majority of their energy from glycolysis, compared to oxidative metabolism in the adult heart [13]. These differences do not disappear immediately following birth. Despite the fact that postnatally human cardiomyocytes have the traditional phenotypic traits of “mature” cardiomyocytes (organized sarcomeres, binucleation, fatty acid as primary energy source), there are still important differences in cardiomyocytes from pediatric hearts compared to cardiomyocytes from adult hearts. One example is that the organization and compartmentalization of components necessary in the intercalated discs demonstrate age-specific differences such that the proteins that make up the intercalated disc are diffusely localized until on year of age [14]. Interestingly, Vreker et al (2014) demonstrate that connexin 43 localization is also age-specific. Another example of age-specific differences is the expression of $\beta 1$ and $\beta 2$ adrenergic receptors where pediatric hearts have greater expression of β -adrenergic receptors than adult hearts. [6]. Thus, it is clear that cardiomyocytes from pediatric patients have a unique phenotype and age-specific molecular mechanisms that distinguish them from cardiomyocytes from adult hearts. To this point, it is highly likely that since molecular mechanisms differ in cardiomyocytes from pediatric hearts, the molecular pathways impacted by disease processes are also different. Characterizing age-specific mechanisms in healthy and failing hearts is critical to develop targeted therapies. At the same time, understanding these distinct molecular mechanisms that occur in pediatric cardiomyocytes may provide insight into specific targetable pathways in cardiomyocytes from adult and geriatric hearts. It is possible that the specific pathways active in pediatric cardiomyocytes impart a novel phenotype that may benefit adult and aging hearts particularly if these mechanisms diverge in response to disease.

As we consider studies using rodent models of disease it is important to recognize that there is a species-specific time frame for cardiomyocyte maturity- with rodent cardiomyocytes maturing in the postnatal period [15] and human cardiomyocytes differentiating in late gestation [16]. This variability in maturation indicates closer study is warranted to understand what molecular mechanisms are at play in which developmental stages. Further, it is evident that while cardiomyocytes from children have phenotypic features that have been traditionally associated with maturity, these cardiomyocytes have unique molecular signaling [4, 6, 17].

3. The aging heart

While pediatric development of the healthy heart has not been extensively characterized, the impact of aging on cardiac remodeling has been described. Even in the absence of systemic factors that adversely impact the heart and vasculature (i.e. hypertension, diabetes), the heart undergoes structural and functional changes with age. In humans, large cohort studies including the Framingham Heart Study and the Baltimore Longitudinal Study on Aging have shown that aging causes an increase in left ventricle (LV) hypertrophy, declines in diastolic function, and diminished systolic reserve in response to exercise [18]. Diastolic dysfunction with preserved ejection fraction- recently designated as HFpEF- is increasing in prevalence in aging populations [19]- especially women- and is a significant cause of hospitalizations in older populations [20]. Age-associated declines in cardiac function have been similarly

observed across animal species including nonhuman primates [21], dogs [22], and laboratory rats and mice [23–25].

In healthy human subjects without overt cardiovascular disease (CVD), myocyte cell diameter increases with age [26]. Similarly, by 18 months of age, C57Bl6 mice demonstrate significant cardiomyocyte hypertrophy [23]. Myocyte hypertrophy likely occurs both in response to increased systemic pressures due to vascular stiffening and age-associated myocyte cell loss. This hypertrophic response is accompanied by myocardial fibrosis, both in laboratory rodents [23, 25, 27, 28] and large animal models including sheep [29] and dogs [30]. Further, gain and loss of function studies in regulators of extracellular matrix synthesis and degradation have supported the conclusion that cardiac aging is characterized by deposition of fibrosis in the myocardium in laboratory animals [31, 32]. Fibrosis in the absence of CVD has been hard to document in humans, but LV collagen levels in human hearts obtained from autopsy without existing disease (67–87 years versus 20–25) demonstrated increased collagen content by Picrosirius red staining and polarized light microscopy [33].

Inflamm-aging, an increase in inflammatory cytokines during the course of the aging process, plays a critical role in various age-associated diseases including cardiac dysfunction [34]. Inflamm-aging is believed to be a consequence of innate and acquired immune system remodeling, resulting in chronic inflammatory cytokine production [34]. Similar to hypertrophy and fibrosis, laboratory animals are good models for studying inflammation associated with aging. A cross-sectional comparison of 69 analytes in adult (7.5 month) and aged (30 month) mice found 26/69 pro-inflammatory analytes to be significantly higher in the plasma of the aged animals, which correlated with increased macrophage infiltration in the LV as well as increased end-diastolic dimensions [35]. A direct role for inflamm-aging in cardiac dysfunction is also evident in several therapies for age-related disease including caloric restriction, the most consistent and robust means to delay aging and improve lifespan. Caloric restriction induces a transcription profile associated with diminished inflammation that mimics a profile like that of an adult heart [36], indirectly suggesting a causal role for inflammation in age-related cardiac dysfunction.

4. Cardiac remodeling across the life-course

4.1 Heart failure in the young

Pediatric heart failure is a low prevalence disease with an annual diagnosis of 1 in 100,000. While rare, pediatric HF has a very high mortality rate and higher cost of care burden due to lifelong treatment [37]. Therapeutic options for pediatric HF patients remain poorly developed. Current paradigms use similar approaches to what is used in adult HF patients, despite the evidence that pediatric HF patients respond differently to therapies [5, 38, 39]. While the 5-year survival in pediatric HF patients is only 50%, pediatric patients are distinct in that a small percentage can recover. Everitt and colleagues assessed echocardiographic parameters in pediatric patients two years following diagnosis of HF. Twenty-two percent of pediatric HF patients recovered systolic function, with younger patients more likely to recover function, suggesting that age at the time of HF diagnosis/development is critical for determination of cardiac function/HF progression/prognosis [40]. This difference may be

due to age-specific molecular mechanisms unique to young hearts. For example, consider the regenerative capacity of the newborn mouse heart. In adulthood, this capacity is lost [41]. Gomes et al compared proteome expression in hearts from adult zebrafish which maintains the ability to regenerate with the proteome from hearts of neonatal and adult mice and concluded that both adult zebrafish cardiomyocytes and cardiomyocytes from neonatal mice express more DNA synthesis-related proteins while cardiomyocytes from adult mice express more mitochondrial related proteins [42]. Further, the myofilament composition of the adult zebrafish and neonatal mouse cardiomyocytes is immature when compared to adult mouse myofilament composition [42]. Understanding the differences between cardiomyocyte cellular mechanisms that occur at different developmental time points will elucidate how the cardiomyocytes respond to stress and may provide insights into molecular targets to induce positive responses in cardiomyocytes from adult and aging patients.

4.2 Heart failure in the aged

Aging is the primary risk factor for HF, with the incidence increasing more than 5-fold during the 7th and 8th decades of life [43]. HF prevalence is only expected to continue to rise, driven by the increasing age of the US population, with projections of more than 8 million people (a 46% increase) expected to be diagnosed with HF by the year 2030 [43]. These astonishing projections are primarily due to the increasing age of the global and American populations, with individuals over the age of 65 the fastest growing population.

Aging can be defined as a “progressive loss of tissue and organ function.” Evolutionary biologist Michael Rose furthered this definition as “a persistent decline in the age-specific fitness components of an organism” [44], suggesting that adaptation to external events (i.e. cell stress, environmental changes, reproductive fitness) declines with age. With this definition in mind, it is not surprising that aged organisms do not tolerate cardiac insult as well as younger counterparts. When subjected to ischemic insult, aged mouse hearts have markedly higher LV end diastolic diameter and volume, as well as significantly lower fractional shortening than young mice [45]. Geriatric human patients are not only more likely to experience a MI than younger adults, but they are also more likely to die as a result of the event, with each year of life associated with a 6% increase in mortality [46]. Similar findings hold true for murine models of pressure overload, with exacerbated global systolic and diastolic remodeling in aged hearts [47]. Thus, from a global perspective, cardiac function is markedly impaired in aged humans and laboratory animals subjected to cardiac insult, often resulting in accelerated pathology or worsened survival in these populations. Aging results in structural and functional declines in other organ systems, potentially exacerbating HF development in the aged populations through extra-cardiac and systemic mechanisms.

4.3 Mechanisms of age-specific remodeling

Since pediatric and geriatric hearts are phenotypically unique from adult hearts, the logical question is does the young/aged heart remodel in a distinct manner from adults? We will discuss three mechanisms of cardiac remodeling that have been well-characterized in adult hearts with HF: hypertrophy, fibrosis, and inflammation. While these are not the only, or even necessarily the most important, mechanisms of cardiac remodeling, they provide a

good platform for the discussion of the impact of age on the remodeling process. Certainly, other pathways including but not limited to, apoptosis and myocyte cell death, angiogenesis, metabolic remodeling, and the transcriptional and epigenetic regulators of these processes, also warrant future discussion and investigation, particularly from the standpoint of pediatric and geriatric heart failure.

Before we can compare the mechanisms of the aged and young heart, it's important to first briefly discuss what occurs in the adult heart. In response to pathological insult such as pathological load or myocyte cell loss, the adult heart hypertrophies. Though initially this response is likely beneficial, sustained hypertrophy becomes maladaptive, resulting in a heart with poor contractile function [48]. Another common response to pathologic insult in adult hearts is fibrosis. Not only an outcome of replacement of damaged myocytes, fibrosis also occurs in response to pressure overload, and is believed to be due to interactions between cardiomyocytes and activated fibroblasts leading to increased deposition of extracellular matrix. The increased extracellular matrix changes the elastic properties of the ventricles and can contribute to diastolic dysfunction [49]. Inflammation is another hallmark of adult HF and is interconnected with hypertrophy and fibrosis where inflammatory cytokines can induce hypertrophy and impact contractile function, as well as activate myofibroblasts, contributing to fibrosis [50]. Overall, even though HF can be induced by a wide-variety of pathologies, adult hearts respond by undergoing cardiac remodeling. These common mechanisms provide important pathways by which to determine if pediatric and geriatric hearts respond to pathology uniquely (Figure 1).

4.3.1 Mechanisms of HF remodeling in the pediatric population: hypertrophy, inflammation and fibrosis—Contrary to the long-held belief that cardiomyocytes hypertrophy occurs in all patients in response to overload, two independent and extensive comparisons of pediatric and adult HF patients clearly demonstrated that pediatric cardiomyocytes do not hypertrophy in HF [4, 7]. Further, analysis of gene pathways that are differentially regulated in pediatric HF compared to adult HF predicted inhibition of hypertrophy in pediatric cardiomyocytes [4]. Patel et al. also associated adult hypertrophied cardiomyocytes with increased sarcomere thickness; however, cardiomyocytes from pediatric HF patients did not demonstrate these changes in sarcomeric thickness. Interestingly, density of myofibrils have been reported to increase in pediatric patients [51], contributing to the overall conclusion that the response of the pediatric myocardium to an unknown pathologic insult is not the same as adults.

Pre-clinically, the data regarding hypertrophic responses of pediatric models are more limited. While there are a few studies in young mice, it is interesting to note that when 4-week old mice are treated with 30mg/kg/day of isoproterenol for a week, heart weight to body weight (HW/BW) does increase (by 9%), albeit less robustly than in 5-month old mice, which show a 25% increase in HW/BW [52]. However, cell size was not measured in this study and it is possible that increased HW/BW in these mice was due to increased cell number. The difference in HW/BW changes between young and adult mice to a known pathologic stress suggests that hypertrophic responses are age-specific.

Despite the knowledge that inflammation plays an important role in HF progression in adults, there is little literature documenting if there are differences in inflammation profiles of pediatric HF patients. Patel et al. reported that genes associated with an inflammatory response are expressed in the LV from adult patients with dilated cardiomyopathy, but not in left ventricles from pediatric patients with dilated cardiomyopathy [7]. Given the growing body of evidence that aging plays an important role in function and profile of the immune system, it is highly likely that pediatric patients have a unique inflammatory profile in HF when compared to adults [53, 54]. One interesting study focused on the immune-response profile in mesenchymal stem cells isolated from rats of different ages. There is a clear delineation between gene activation, cytokines, and miRNAs in each of the age groups (newborn, infant, young, prepubertal, pubertal, and adult) [55]. Since inflammation plays such an important role in adult and geriatric HF, it is logical that it may play a role in pediatric HF; therefore, understanding how inflammatory profiles change with age is critical to provide the best care and address factors that contribute to disease progression. In addition, understanding age-specific differences in the immune system are also critical when considering immunosuppressive therapies required following transplantation [56].

Fibrosis is associated with pathology in the heart and fibrotic changes that occur can exacerbate dysfunction by increasing ventricular stiffness. However, pediatric HF patients do not develop fibrosis to the same extent as adult HF patients [7, 57]. In fact, analysis of the gene expression of metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) is different in pediatric HF patients and adult HF patients [57]. This difference may be due to the disease pathogenesis; these studies have focused on pediatric patients with HF due to unknown pathogenesis. It is not known if the lack of fibrotic response in pediatric hearts in response to pathology contributes to poor outcomes or if it is an age-specific advantage that contributes to the capability of pediatric patients to recover. Further studies into differential responses that occur in pediatric HF patients when compared to adult HF patients may inform potential targets.

4.3.2 Mechanisms of HF remodeling in the geriatric population: hypertrophy, inflammation and fibrosis—Somewhat surprisingly, given the exacerbated global dysfunction regularly reported with aging and the increased LV thickness associated with aging per se, hypertrophy is generally diminished in aged models subjected to cardiac insult. Fisher 344 Brown Norway rats at two ages (7 and 18 months) were subjected to myocardial infarction (MI) and studied 5 months later. Despite similar infarct sizes, myocyte cross sectional area increased in younger rats, as expected, but was unchanged in 23-month old rats [58]. This finding is consistent with a renal artery constriction model of hypertension, where heart weight increased by 50% at 5-months of age in response to the hypertensive insult, but only 12% at 20 months of age [59]. Hypertrophy is blunted even when aged models are subjected to age-adjusted relative pressure overload, as in the case where 9, 18, and 22-month old Fisher rats were subjected to transaortic constriction (TAC) based on similar relative constriction (not a given level of LV pressure, due to increases in LV pressure with age). LV/tibia length and myocyte width increased in 9-month old rats, but did not increase with TAC compared to sham controls in 22-month old rats [47]. These authors followed-up this work with an investigation on the impact of volume overload on

hypertrophic remodeling, and again, following surgical aortic insufficiency, found that by 4 weeks post-surgery, aged rats had higher LV wall stress, worsened LV end diastolic pressures, higher lung fluid retention, but with no changes in LV hypertrophy [60]. The underlying basis for this attenuated hypertrophic response remains unknown, though it has been proposed that an impaired response of the aged myocardium to pressure or volume overload might result in persistent elevation of intra-cardiac pressures and wall stress, contributing to adverse ventricular remodeling. It is possible that aged myocytes have reached their size limit due to aging, and cannot hypertrophy in response to overload [61].

As discussed above, inflamm-aging contributes to tissue dysfunction in a variety of organs, including the heart. This chronic inflammatory state, coupled with myocyte cell loss, likely also contributes to deposition of fibrosis, resulting in the mechanically dysfunctional, stiff heart which is associated with the aging cardiac phenotype. Alongside the chronic inflammatory state, however, is a deficit in the capacity for appropriate injury response, including activation and resolution of inflammation. This impairment is most evident in the setting of post-MI remodeling. Adult (2–3 months) C57Bl6 mice undergoing coronary artery occlusion and reperfusion demonstrate early infiltration of the infarcted myocardium with neutrophils, followed by resolution. Aged (>2 years) mice, however, have reduced peak neutrophil density, attenuated macrophage infiltration, and diminution of chemokine and cytokine induction (MCP-1, MIP1b and 2) compared to adult mice [45]. In this case, attenuated inflammation in response to tissue injury may prevent the heart from beneficial adaptation to cardiac insult in the short-term, and therefore have long-term maladaptive impact on cardiac function [62]. As might be expected in aged models with attenuated inflammatory responses, chronic post-MI fibrotic remodeling is also diminished. Five months following MI, 7-month old rats demonstrate predicted increase in fibrosis as assessed by Picosirius red staining, while 23-month old rats do not. Correlative analysis suggested that the negative interaction of aging and MI on fibrosis was highly significant [58]. Defective fibrotic tissue deposition in the aged heart may be due to impaired response of aged fibroblasts to growth factor stimuli, as evidenced by attenuated phosphorylation of Smad2 following stimulation of TGF- β 1 in aged cells compared to those isolated from young animals [45]. The blunted response of aged fibroblasts to fibrogenic mediators is not limited to TGF- β stimulation, as stimulation of isolated Wistar rat fibroblasts from aged hearts (24 month) compared to fibroblasts isolated from adult hearts (2–3 months) have attenuated matrix synthesis in response to angiotensin II [63].

Investigations of the interaction between age and post-MI remodeling in humans have focused on systemic, not cardiac-specific, inflammation. Mahara and colleagues looked at post-MI systemic inflammatory responses in patients prospectively admitted to coronary care units for primary angioplasty grouped by age as younger or older than 70. They assessed acute C-reactive protein and interleukin-6 (IL-6) plasma values 6 months following acute MI and found both inflammatory markers were higher in older patients (who also had worse adverse LV remodeling and higher incidence of heart failure) [64]. Thus, in humans, exacerbated inflammation may be present systemically in aging populations with HF, though this conclusion warrants future investigation. Certainly, it has been well-established in aging humans that systemic inflammation is exacerbated compared to adults; however, the interaction between disease and cardiac insult (prolonged/elevated or diminished) remains to

be determined. These investigations are limited by methodological difficulty in studying the aging human myocardium and the fact that aged patients are underrepresented in randomized controlled trials [65].

At baseline, inflammatory cytokines are elevated in elderly patients without history of MI [66]. Further, manipulation of these inflammatory pathways in pre-clinical models of pressure overload such as TAC attenuates cardiac remodeling [67]. However, primary investigations of the impact of age per se on these pressure overload remodeling pathways are sparse with regard to inflammation. Regarding the impact of age on non-MI fibrotic remodeling, in a deoxycorticosterone acetate (DOCA)-salt model of hypertension, fibrosis was assessed in 24-month old rats both histologically and by hydroxyproline assay. Though age-induced increase in fibrosis was observed, DOCA-salt treatment in aging did not further impact fibrotic remodeling, as aged rats did not develop additional fibrosis as assessed by expression of type I or III collagen [27, 68]. Similar findings have been reported in a sheep model of right ventricular tachypacing in adult (18–24 month) and aged (>8 years; average sheep life expectancy 6–11 years) sheep. As expected, cardiac dysfunction was worse in aged sheep, with proportionally greater deficits in fractional shortening and LV chamber diameter. However, while collagen accumulated as expected in the adult tachypaced HF group, collagen deposition was lower in the aged HF sheep. These changes in collagen deposition also coincide with dysregulation of matrix metalloproteinase and tissue inhibitor of metalloproteinase expression [29], further supporting the notion that inflammatory-fibrotic remodeling in the aged heart is importantly different and attenuated compared to adults.

5. Sex differences across the life-course in HF

This review thus far has focused on age as a biological variable. However, a successful life-course approach to understanding and treating human disease should also include an analysis of the impact of sex on disease mechanisms. Largely, the discussion of how sex impacts HF has been discussed from a pre- and post-menopausal standpoint, based on consistent observations that HF incidence and prevalence significantly change at menopausal age [43]. While this delineation is not fully incorrect or unwarranted, this approach is too simplistic for several reasons which we will briefly discuss below.

In the pediatric population, specifically in pre-pubertal children with dilated cardiomyopathy, female sex is a risk factor for adverse outcomes [69]. Other than this epidemiological observation, however, very little is known regarding sex differences in terms of pediatric HF. Based on the fact there are outcomes differences, sex is important to consider in pre-pubertal children and should be further studied. In addition, there also are overt sex-differences in adolescent hearts. Kapuku et al reported that there are differences in diastolic function between healthy girls and boys (ages 14–18) in that geometry of the LV and filling pressures in girls suggest they may be more prone to developing diastolic dysfunction [8]. Taken together, this data support the need for future studies to assess sex differences in all age groups, including pre-pubertal groups previously thought to be less impacted by circulating sex hormones.

HF epidemiology demonstrates a clear protection against CVD and HF outcomes in premenopausal women who have a better prognosis than men. Pre-clinically, laboratory rodent studies often model menopause with ovariectomy, a rapid surgical removal of ovarian estrogen. While this model allows the mechanistic investigation of the impact of ovarian estrogen on cardiac and cardiovascular remodeling, it is not directly relevant to human life-course changes. In humans, menopause is a decade-long transition with progressive decrements in circulating estrogen, mirrored by progressive decrements in cardiovascular-related phenotypes across the menopause transition [70]. Therefore, even within a cohort of 49–65 year old women, there are significant phenotypic differences. These observations are supported by investigations of age at menopause and HF outcomes, where women who enter menopause at an earlier age have increased risk for developing HF [71]. Furthermore, HFpEF, a true geriatric syndrome, presents with significant sex differences, with prevalence, pathogenesis and therapy differing between sexes [72], despite the fact that the HFpEF patient population is nearly exclusively postmenopausal. Together, the sparse data in pediatric populations and post-menopausal aged individuals highly suggests that sex is an important biological variable in the HF life-course. Sex-specific investigations of cardiac remodeling in these patients is warranted, in addition to the comparison of older and younger boys/men to determine what impact sex plays in cardiac remodeling in the absence of sex hormones.

6. Harnessing mechanisms in the young heart for treatment of the aged heart.

Although more work remains to be done to elucidate the underlying mechanistic and signaling pathways, it seems that induction of three hallmarks of cardiac remodeling- hypertrophy, fibrosis, and inflammation- are diminished in pediatric HF. Interestingly, even though the geriatric heart is significantly more susceptible to cardiac stress and undergoes more severe remodeling, these hallmarks are also attenuated in the geriatric heart (Figure 1). Even though the molecular pathways of hypertrophy and fibrosis appear similar between the youngest and oldest HF patients, their global remodeling and clinical outcomes differ greatly. While pediatric patients occasionally spontaneously recover, this phenomenon is completely absent in elderly patients with HF. It's unclear from current literature why the youngest and oldest patients respond differently to cardiac stress than adults. Presumably, transcriptional and epigenetic regulators vary by age, and may be responsible for the differential activation of hypertrophic, fibrotic, and inflammatory outcomes. These findings highlight a need to better understand the signaling cascades, transcription factors, and molecular mediators of pediatric and geriatric cardiac remodeling.

Not only will understanding the unique age-specific mechanisms of HF remodeling facilitate better design of therapeutics, but it is possible that identification of molecular signaling pathways that are differentially regulated during pathologic insult in pediatric hearts and adult or geriatric hearts could yield valuable insight into prevention/resolution of these remodeling events (Figure 2). The pediatric heart is phenotypically more resilient, especially when compared to the aged heart [73]. Conceptually, the enhanced resilience during the postnatal period could be attributed to “juvenile protective factors”- physiological factors

intrinsic to pediatric organisms which diminish or disappear throughout maturation (National Institutes of Aging). Diminution or disappearance of these factors may then contribute to, or at least predispose, the adult and geriatric heart to age-related declines in function. Proof of concept for this idea stems from heterochronic parabiosis experiments, where animals of two disparate ages (young or aged) are joined to share circulation. Similar models of surgical tissue transplantation with transplanting of young tissue into an aged animal also restores tissue declines with age [74, 75]. These types of experiments have identified putative candidate juvenile protective factors used to “rejuvenate” target issues in aged models. One such factor is growth differentiation factor 11 (GDF11). GDF11 protein circulates at high levels in neonates and pediatric populations and declines dramatically with advancing age. Increasing levels of circulating GDF11, such as through heterochronic parabiosis, rescues some phenotypes of cardiac aging [76]. Though these findings are not without controversy [77], they do highlight the potential for specific factors unique to young organisms to “rejuvenate” the aging heart. To answer these questions or identify the resilient phenotype of the young heart, several questions remain. At what age(s) does the pediatric/ juvenile resilient window exist? Which tissues or specific cell types may contribute to the resilient phenotype? Does sex as a biological variable modify or impact the resilient phenotype? Answering these questions and more, using a life-course approach from development to aging, will help identify strategies for the aging heart.

7. Conclusions and Future Research

HF remains an enormous public health concern, impacting patients across the human life-course from birth until death. Treating pediatric populations with adult therapeutics has not proven successful, nor have 5-year survival in adult/aging HF trends markedly improved, despite significant clinical and scientific efforts. We propose this is in part due to age-specific differences in these patient populations, which greatly differ compared to the adult heart with regard to hypertrophy, inflammation, and fibrosis. Understanding the mechanisms underlying pediatric and geriatric heart failure will not only improve therapeutic outcomes in these populations but will also lay the foundation to identifying juvenile protective factors which characterize the resilient phenotype of pediatric organisms. Further, consideration of life-course changes in behavioral and social contributors to HF development will likely also facilitate more effective therapeutic approaches. Despite growing evidence that developmental factors in early life can influence health and disease later in the lifespan, development and aging continue to be studied separately. Thus, future research using a life-course approach is needed.

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Highlights

- Heart failure impacts patients across the life-course, from pediatric to elderly patients
- Cardiac remodeling in the pediatric and aged hearts are not the same as adults
- Understanding age-specific remodeling may improve therapy

Figure 1.
Age-specific differences in cardiac remodeling following pathologic insult.

Figure 2.

Proposed identification of juvenile protective factors present in pediatric hearts/circulation for development of new therapeutic targets for cardiac resilience in aging patients.