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STATE-OF-THE-ART REVIEW

GERIATRIC CARDIOLOGY

Born to Age: When Adult Congenital Heart Disease Converges With Geroscience

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ABSTRACT

Advances in imaging, catheter-based interventions, congenital heart disease surgery, and clinical management of congenital heart disease (CHD) have yielded a dramatic change in age distribution of the CHD population. This implores clinicians and researchers to gain a better understanding of aging, as this will be the cornerstone to how we plan and manage this rapidly evolving group of patients. In this article, we first review the demographic changes in the CHD population and then describe the systemic complications of disease observed in young patients with CHD, following which we discuss general concepts in aging that may be transferable to the CHD population. Finally, we review inflammation and its potential impact on aging. We provide a new lens on aging in CHD and its functional consequences in CHD, with the goal of stimulating an exchange of knowledge between geroscientists and CHD. (JACC Adv 2022;1:100012) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Challenging us to care for life from the womb to old age, the changing demographics of congenital heart disease (CHD) provides a powerful opportunity to reorient our understanding of aging in the CHD population.[1] Oscillating between disease and health, CHD trajectories encompass the life span.[2] The last 2 decades have seen rapid growth in the number of studies dedicated to the documentation of the rise in the number of adults with CHD, the complications that are observed as patients age, and the number of guidelines generated by national and international expert groups on how to manage adults with CHD. As we observe the number of adverse complications associated with increased longevity, the question becomes, can outcomes be changed? As cardiovascular disease (CVD) becomes detectable sooner and advances in therapies enable longer life, the question of biological versus chronological age is coming increasingly into focus. Nowhere is this truer than for CHD where we see young patients with old hearts. Adverse anatomic and hemodynamic complications that occur in the womb persist and become complicated with superimposed acquired CVD for as long as longevity permits.[1] Too often reassured by the young age of our patient population, we fail to understand the burden of the biologic debt that a longer life incurs.

In this article, we address the question: How should the age be measured in patients with CHD? We submit that, for long-term outcomes to change, a shift in paradigm needs to occur in the tools we use to

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ABBREVIATIONS AND ACRONYMS

ACHD = adult congenital heart disease

BMI = body mass index

CAD = coronary artery disease

CHD = congenital heart disease

CVD = cardiovascular disease

LDIR = low-dose ionization radiation

suPAR = soluble urokinase plasminogen activator receptor

TOF = tetralogy of Fallot

assess age. We first review the demographic changes that underpin our clinical inquiry, the systemic complications of disease observed in our young patients and subsequently we review, largely from non-CHD literature, concepts in aging that may be transferable to our population to provide a new lens on aging in CHD. Finally, we review inflammation and its potential impact on CHD, amplified by the growing body of evidence, an unequivocal by-product of the ongoing COVID-19 pandemic, that will profoundly affect our understanding of biology for decades to come.

HIGHLIGHTS

- The population of patients with CHD is aging, as demonstrated by the changing demographics.
- A accumulation of cardiovascular and systemic complications is prevalent in CHD.
- Concepts of geroscience, such as frailty and sarcopenia, are slowly finding their way to CHD.
- Scientific evidence on functional and biological markers of aging in CHD is highly needed.

CHANGING DEMOGRAPHICS IN CHD

The changing age distribution of CHD motivates us to evolve our understanding of aging in the CHD population and is cornerstone to how we plan and manage this rapidly evolving, fascinating group of patients. Data supporting the shift in demographics began to emerge between 2000 and 2010. On a population level, a rising prevalence of CHD in adults compared to children from 1985 to 2000 was observed, such that by 2010, the numbers of adults with all forms of CHD exceeded the numbers of children, with fully two-thirds of the population being adults.[3,4] Using comprehensive population data sources, the life span prevalence rates of subjects with CHD was documented: 8.12 per 1,000 at birth, 13.11 per 1,000 in children, 6.12 per 1,000 in adults, and 3.7 per 1,000 in geriatric populations older than 65 years, thus warranting coining the term "Geriatric Adult Congenital Heart Disease".[5] In the U.S, a number of methods have been and are being used to generate direct empirical measures of adult coronary heart disease (ACHD) populations.[6,7] Working with the Centers for Disease Control and Prevention, we generated first-time empirical estimates of the changing profile of the CHD population in the U.S. Of an estimated total of 2.4 million subjects in the U.S. with CHD, 1.4 million were adults, while 1 million were children in 2010.[8] Obtaining prevalence rates of 6.16 per 1,000 adults older than 18 years, there were, as generated by empirical estimates in 2010, a total of 160,000 adults with severe CHD compared to 123,000 children with severe CHD, underscoring the fact that the responsibility of patients with CHD is well anchored in adult cardiology practice.

In summary, advances in surgical and clinical management of CHD have allowed over 90% of children to survive to adulthood.[9,10] However, this development has led not only to a shift but also to a swelling in mortality into adulthood.[11] Nonetheless, by 2030, it is estimated that 11% of the adult CHD population will be aged 60 years or older.[12] The first empirical data show that older persons with CHD constitute a specific group of individuals with high morbidity, health care utilization, and mortality.[5,13-15] Thus, there is evidence to support the notion that there is a growing demographic of ACHD in geriatric populations, but the question raises if "geriatric" ACHD is confined to those older than 65 years.

DEFICIT ACCUMULATION ACROSS THE LIFE SPAN OF PATIENTS WITH CHD

Although chronological age is typically linked with health decline, as the U.S population ages, it is becoming increasingly clear that people can live beyond the eighth decade with good health.[16] As demographic shifts in aging populations occurred in the latter half of the 20th century, the "old-old" and the "young-old" were terms introduced to highlight the decoupling of the chronological age and disease burden that impacts functional status.[17] In this review, we ask how young can the "young-old" be? What evidence is there to suggest that the increased longevity of the CHD population is associated with the increasing disease burden of multisystem disease at a young age?

CARDIOVASCULAR COMPLICATIONS IN CHD. Prolonged time windows to amplify the expression of ventricular dysfunction, hemodynamic dysfunction, and arrhythmia play an important role in ACHD outcomes. Over a 30-year time period, nearly one-quarter of people with ACHD will develop heart failure.[18] Precipitating factors include myocardial dysfunction, valvular disease, shunts, and arrhythmias. Heart failure with reduced ejection fraction is

commonly seen in patients with a morphologic systemic right ventricle or a single ventricle after Fontan palliation, and heart failure with preserved ejection fraction is also becoming increasingly recognized.[19] Fontan failure with preserved ejection fraction remains one of the most challenging types of circulatory failure to treat.[20] Reoperations for significant residual valvular dysfunction are most commonly indicated for pulmonary regurgitation in tetralogy of Fallot (TOF) or tricuspid regurgitation in patients with congenitally corrected transposition of the great arteries to preserve or reverse myocardial impairment.[21] Arrhythmia is a common indication for hospitalization and cause of death in ACHD, with more than half the patients expected to develop an atrial tachyarrhythmia during their lifetime.[22] In a retrospective cohort of 44,880 patients with CHD followed up from 1985 to 2005, we have shown that a 20-year-old patient with CHD has the same risk of developing atrial fibrillation to a 55-year-old without CHD.[23] Furthermore, there is a 2 to 5% incidence per decade of sudden cardiac death in individuals with TOF and transposition of the great arteries after atrial switch.[22,24]

Population studies have found that the cumulative incidence of myocardial infarction in ACHD is 7.5% by the age of 65 years.[25,26] Patients with CHD have a 1.5 to 3 times higher risk for coronary artery disease (CAD) than non-CHD individuals.[25-29] In younger age cohorts, the relative risk to develop myocardial infarction is even 16 times higher,[30] irrespective of the crude incidence being low.[29-31] A large part of the patients, however, have subclinical CAD. Selective coronary angiography for other reasons than suspected or known CAD showed that 9.2% of adults with CHD had ≥1 stenosis of more than 50% in a major coronary artery, which was not predicted in a patient with a history of chest pain.[32] About one-third of patients with angiographically confirmed CAD is asymptomatic.[31] Surprisingly, the incidence of CAD seems to be higher in patients with simple CHD than in those with more complex heart defects.[28,32] Even patients with simple heart defects have a 2.6 times higher risk of having CAD.[33]

Cardiovascular risk starts early in CHD and continues for the decades that longevity currently permits. Obesity and anthropometric trends on longitudinal follow-up of children with CHD reveal a steady rise in body mass index (BMI) between childhood and adolescence.[34] At a median follow-up of 7 years in 725 patients with repaired CHD, up to one-third of patients had an increase in BMI between the ages of 2 and 18 years, indicating the early onset of adverse risk factors for CVD.[34] Metabolic syndrome has also been increasingly recognized in young ACHD populations. A study from Seattle compared 448 adults with CHD with 448 controls matched on age and sex, finding that at a mean age of 32 years, metabolic syndrome was twice as prevalent in the CHD population.[35] In a cross-sectional study of 160 patients who underwent coarctation repair, from 1974 to 2009, patients were found to have a significantly greater BMI and blood pressure than controls as early as 5 years and up to 20 years following repair.[36] Type II diabetes occurred more frequently in a sample of 135 patients with CHD with a mean age of 48 years in South Korea (38.5%) than in nonafflicted controls (30.3%).[37] In a Danish population-based cohort, over 5000 patients aged 30 years or older were observed.[38] The risk for developing diabetes was 1.35 times higher in patients with CHD vs people from the general population.[38] Thus, not surprisingly, in a retrospective cohort study of 3,239 geriatric adults with CHD we have shown a high prevalence rate of diabetes (16%).[5]

CHD COMPLICATIONS BEYOND THE HEART. The aforementioned data showed that we have young patients with old hearts. This raises the question, do we also have young patients with old brains? Although neurodevelopmental delays have been well described in children with CHD,[39] when abnormal neurodevelopment in a child does become neurocognitive decline in an adult?[40] There is significant research on the prevalence and types of neurodevelopmental disabilities in children and young adolescents and a growing body of evidence on the impact of CHD on the brain of adults with CHD.[41] Cumulative cardiovascular injuries are seen as an important cause of neurocognitive impairment in CHD.[40,42,43] Midlife cardiovascular risk factors including obesity, diabetes, hypercholesterolemia, hypertension, and smoking have an impact on the development of late-life cognitive decline, as shown in non-CHD populations.[44,45] What then might we hypothesize in patients with CHD who have early exposure to cardiac disease and early onset of CVD risk factors? Knowing that acquired cardiovascular risk factors play an important role in the development of cognitive decline, it could be expected that this may be more prevalent in people with CHD. To date, only one study investigated the prevalence of "dementia" in a population-based cohort.[46] In this study, the term was used generically rather than specifically in a clinical diagnosis setting. The cumulative incidence of dementia in CHD at the age of 80 years was 4%. However, this figure is likely to be subject for

survivorship bias because the cumulative mortality at 80 years in CHD is 60%. The risk of developing dementia was 1.6 times higher in people with CHD than in the general population. In people aged 64 years or younger, the risk was up to 2.6 times higher, indicating that dementia occurred more often and sooner in people with CHD than in nonafflicted people. The risk for stroke was 1.5 to 5 times higher than in age-adjusted controls.[29,33,47-51] In younger cohorts of patients with CHD, the relative risk was even up to 12 times higher than in their age-matched controls.[50,52] Ischemic stroke occurred about 15 year earlier in people with CHD than in the general population.[47,51] The median age of developing ischemic stroke in CHD was about 50 years, whereas in the general population, this is between 65 and 70 years of age.[47,50,51] Also in patients with simple CHD, stroke occurred frequently, mainly in association with untreated shunts.[33,52] Additionally, over one-third of adults with CHD reported a mood or anxiety disorder.[53] Both cognitive challenges and psychosocial distress can have profound effects on patients with CHD health care, education, employment, and overall quality of life.

Increasingly, the complications at distance from the heart are leading to the recognition of ACHD as a multisystem disorder.[54] Up to half of adults with CHD are noted to have abnormal lung and kidney function.[55,56] In hospitalized patients, noncardiac conditions more than doubled from 1998 to 2010.[57] Restrictive lung disease, renal dysfunction, anemia, and liver cirrhosis have all been associated with reduced survival in adults with CHD.[58] Not surprisingly, noncardiac morbidities increase the risk of acute kidney injury, pneumonia, and respiratory failure post-operatively.[48] In patients with genetic syndromes, endocrine and immunologic complications are seen.[59] Indeed, while multisystem complications suggest accelerated aging in people with CHD, it is indicated that the presence of genetic syndromes even further accelerate the aging process. In people with trisomy 21, accelerated aging and immunosenescence are well documented.[60] The Williams-Bueren syndrome is another genetic condition with multisystemic involvement characterized by early aging, dementia, autoimmunity, and chronic inflammation.[61] Women with Turner syndrome are found to be more susceptible to develop arterial hypertension, osteoporosis, sensorineural hearing loss, diabetes mellitus type 2, or thyroid disease.[62] Patients with TOF and 22q11.2 microdeletion have been found to have higher mortality rates than TOF patients without microdeletion.[63,64] This also suggests the additional burden of genetic disorders on aging and patient outcomes.

During adult life, an exponential growth in cancer has been observed in people with CHD. By the age of 15 years, the cumulative incidence of cancer was reported to be about 0.9%.[65,66] The cumulative incidence increased to 4.5% by the age of 40 years[66] and 15.3% by 64 years.[67] The risk of developing cancer was 1.65 to 2.24 times higher in people with CHD than in the general population,[65,66,68] with cancer reported to be the second leading cause of noncardiovascular death in adults with CHD.[69] Risk factors include prior radiation exposure, with the effect being modified by genetic factors. Specific conditions, such as Fontan palliation, have been associated with hepatocellular carcinoma.[58] The impact of exposure to low-dose ionization radiation (LDIR) in children with CHD and the late observation of premature cancer in ACHD populations constitute another example of how early exposure to injury results in late complications of disease. Children with CHD are exposed to LDIR from cardiac procedures not only at increasingly higher doses in recent years but also at progressively younger ages.[70] Thus, the increase in cancer rates observed beyond the syndromic associations well described in the literature may be directly related to LDIR exposure in this population.[66,67]

In summary, there is a rapidly growing body of evidence that CHD in adults is a multisystemic condition with an increasing deficit accumulation as patients age and complications migrate from the heart to the rest of the body. From the womb to old age, the convergence of deficit accumulation onto heart lesions that are congenital amplifies the impact of survival that CHD now permits. Nowhere is it clearer that the rate of aging varies substantially across CHD populations. How then do we link deficit accumulation to health decline in aging CHD populations, and what novel metrics have been or should be explored?

MEASURING AGE IN CHD

THE RATE OF AGING: CAN IT BE CAPTURED?

Quantifying biological age in our young adults with CHD offers novel opportunities to reframe our concept of age and operationalize evolving measures in geroscience to inspire our understanding of long-term outcomes in CVD at large. In a study published in the Proceedings of the National Academy of Science, a group of international experts observing the rapid graying of populations across the globe asked the question: are young adults aging at different rates?[71] It follows that from this perspective, the question is really, if young age is too soon to start thinking about how to prevent aging, or better yet, how can premature aging be prevented to promote

health. Highly relevant to clinical inquiry in our own field, this thought-provoking question deserves to be examined. Published in 2015,[71] the group studied a population of 1,037 young adults comprising cohorts born from 1972 to 1973 followed up from birth to age 38 years, strikingly similar to the demographics of patients with severe CHD.[4,72] The study outcomes were comprehensive including biological, physical, and psychosocial measures of aging. Biological age was measured using the National Health And Nutrition Examination Survey-based measure validated in the U.S., which outperformed chronological age in predicting mortality.[73] Relevant to CHD populations, a composite panel of markers was used to define a "Pace of Aging" outcome including cardiorespiratory fitness, lung function, leukocyte telomere length, morphometrics, creatinine clearance, cholesterol and lipoproteins, and HbA1C that were measured at age 26, 32, and 38 years. A clear increase in biological age correlated with an acceleration of the Pace of Aging index in the prior decade, indicating that biological age can in fact be predicted. Moreover, subjects with advanced biological age had diminished physical capacity as measured by hand grip, balance, and other motor test as well as cognitive assessment tools, highlighting the importance of biological age as an outcome measure.[71] Provocatively, it illustrates that even in nondiseased populations, different rates of aging can be observed as early as the third decade of life. One can only guess what a similar study might reveal in our own CHD patients.

INTEGRATIVE MEASURES OF AGING. Beyond chronological age, several integrative measures of aging have been studied in geroscience,[74] from which we may be inspired to quantify aging in persons with CHD. These include measures of frailty and sarcopenia, telomere length, DNA methylation clocks, and aging biomarkers.[74]

The concept of ***frailty*** was introduced in the 1970s by statistical demographers specifically to account for the different rates at which people age. It is fascinating to note that the process of deficit accumulation is exponential, detectable as early as 15 years of age and doubling every 15 years with the final doubling time near the end of life, in non-CHD populations between the ages of 70 years and 90 years as determined in a National Health Survey of over 14,700 Canadians between the ages of 15 and 102 years.[75] Frailty is defined as "*a significant decline in functional reserve, resistance, and resilience of multiple organ systems, and the resultant extreme vulnerability of the individual to endogenous and exogenous stressors (like infection, injury or surgery, or some medicines), leading to a higher risk of accelerated functional decline and adverse health-related outcomes*".[76]

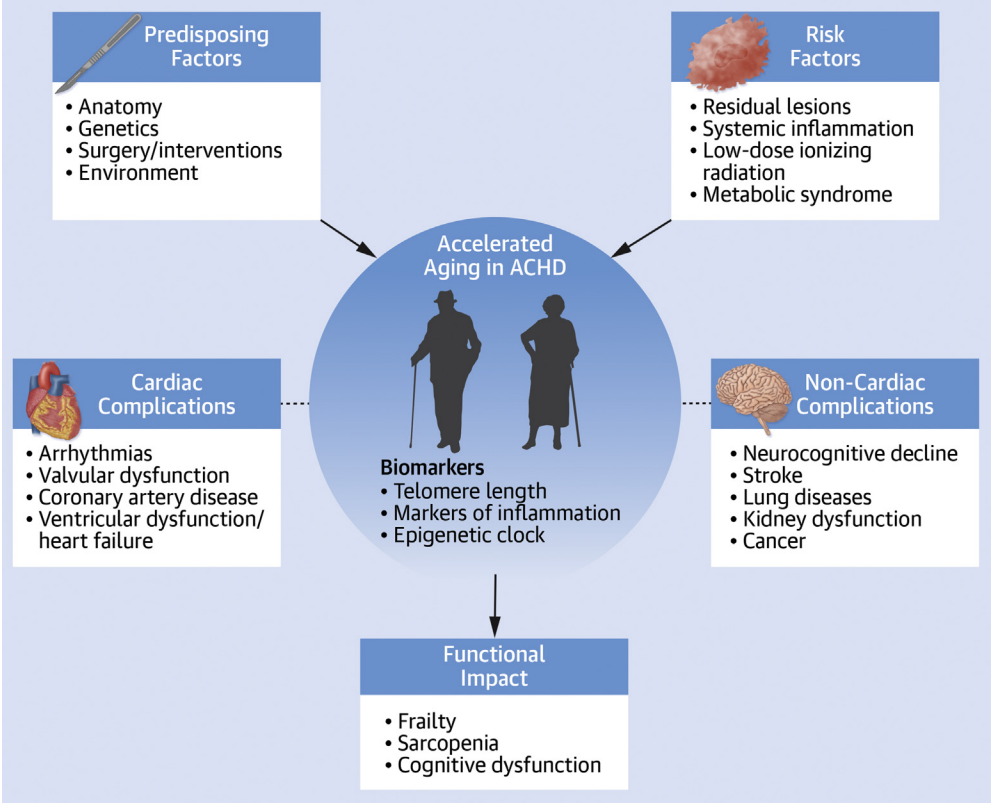
There are two main models to operationalize frailty. A first model was developed by Fried et al., who operationalized frailty as a distinguishable clinical phenotype. In this model, frailty is characterized and composed by: 1) unintentional weight loss (including loss of muscle mass); 2) weakness; 3) exhaustion; 4) slowness; and 5) low activity level.[77] People who score positive on 3 or more criteria are considered to be frail, people with 1 or 2 positive criteria are considered to be pre-frail, and people with no positive criterion are nonfrail.[77] The Fried phenotype method requires an in-person assessment. Therefore, it is suitable to be used in clinical practice.

Another model is the Rockwood accumulative deficit model.[75] This method operationalized frailty by cumulating deficits such as : 1) diseases that are seen in older (eg, diabetes; hypertension) and non-older persons (eg, asthma; food allergy); 2) sensory alteration and symptoms (eg, impaired hearing); and 3) disabilities (eg, assistance needed to prepare meals). A frailty index is calculated by counting the number of deficits and dividing this count by the total number of deficits considered, resulting in a theoretical range of 0 to 1.[75]

Frailty is already well investigated in cardiac populations. The empirical evidence is so extensive that systematic reviews and meta-analyses could be made on the predictors and outcomes of frailty in CAD,[78] heart failure,[79,80] atrial fibrillation,[81] hypertension,[82] in-hospital cardiac arrest,[83] percutaneous cardiac interventions,[84] cardiac surgery,[85] and transcatheter aortic valve implantation.[86] Frailty is obviously strongly related to age. However, also in nonelderly cardiac patients, frailty is prevalent.[87] There is growing evidence that the relationship between frailty and CVDs is bidirectional.[88] Frailty is both a predictor of CVD and an effect modifier in those with CVD (**Central Illustration**).

To date, frailty has not been comprehensively investigated in CHD. However, in the international APPROACH-IS II (Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart disease-International Study 2) project that is currently running, frailty is assessed in patients with moderate or complex CHD aged 40 years or older, using the Fried method (NCT04902768). Preliminary analyses on 79 patients from Belgium showed that

CENTRAL ILLUSTRATION Aging in Congenital Heart Disease



Moons P, et al. JACC Adv. 2022;1(1):100012.

41.8% were in a pre-frail status and 8.9% were frail (data on file). In the age cohorts of 40 to 49, 50 to 59, and 60+ years, frailty was observed in 0%, 10%, and 21.7%, respectively. Final data from the APPROACH-IS II project, obviously, will yield more generalizable findings.

Sarcopenia is defined as the age-associated loss of skeletal muscle mass and function.[89] It is characterized by the degenerative loss of skeletal muscle mass, quality, and strength.[90] Primary sarcopenia is age-related, when no other specific cause is evident.[90] Secondary sarcopenia occurs when secondary causes, other than or in addition to aging, are evident.[90] The link between frailty and sarcopenia has been debated in geroscience,[75,77] but it is reasonable to accept that sarcopenia may constitute an determinant of frailty.[89] In CHD, secondary sarcopenia has been observed, probably as a result of the systemic impact of the heart defect and the aforementioned age-related morbidities. A study that included patients with simple and complex CHD with a mean age of 37 years found a prevalence of sarcopenia of 16.2%.[91] Another study, in which only complex heart defects with a mean age of 36 years were included, found a prevalence of 50.7%.[92] This high prevalence of sarcopenia consistent with the impaired skeletal muscle function has been previously observed in complex CHD.[93] This is probably due to altered muscular oxygenation kinetics.[94] The prevalence of sarcopenia was higher in women with CHD than in men.[91,92] In a single-center study of sarcopenia, 67 Fontan patients, of whom 17 had abdominal CT scans, were compared to 125 age-matched healthy controls and 425 elderly patients undergoing a transaortic valve replacement (TAVR).[95] The male subgroup with a mean age of 24 years with Fontan has a psoas muscle area that was not significantly different from that of the TAVR group with a mean age of 85 years but was significantly lower than that of the healthy controls with a mean age of 30 years.[95]

A plausible biological marker for accelerated aging is the *telomere length*. Telomeres are the ends of

chromosomes that comprise a cap of noncoding DNA (TTAGGG repeats) and that protect chromosomes from degradation and prevent fusion with neighboring chromosomes. Telomeres shorten with each cell cycle, making them good markers of overall cellular replicative capacity and senescence. Telomere length is both a marker of aging and a cause of age-associated diseases.[96] The telomere shortening process can be accelerated by environmental and lifestyle factors, many of which increase oxidative stress levels and inflammation.[97] Examples of determinants of telomere shortening are exposure to LDIR,[98] sedentary lifestyle,[99,100] overweight,[101] depressive mood,[102,103] perceived stress,[104] and living alone/loneliness.[105,106] These factors are known to be prevalent in the CHD population. A large proportion of patients even may have an accumulation of these risk factors.

To date, one study has investigated telomere length in people with CHD.[107] This study found that the telomeres are 23% shorter in adults with CHD (mean age: 25 years) than in healthy controls. An inverse correlation between leucocyte telomere length and the cumulative radiological effect dose was confirmed.[107] The accelerated telomere shortening may already have started early in life. A study in children with critical illness, who had a median age of 4.5 years and half of whom had cardiac diseases, showed that telomeres in patients were 6% shorter than in healthy children.[108] This suggests that very early adverse childhood experiences, such as undergoing cardiac surgery or physiologically adapting to the CHD, may already trigger an accelerated process of aging. Parenteral nutrition in these critically ill children was found to have an extra deleterious effect on telomere length.[108] The role of other more generic risk factors has not been investigated in CHD to date.

A novel and complementary way to scrutinize and understand the disparity between rates of chronological and biological aging is determining the *epigenetic clock based on DNA methylation*.[109,110] Methylation yields a chemical modification of DNA, which regulates gene expression. There are particular DNA methylation patterns at specific genomic regions that are associated with aging.[111] The impact of environmental, behavioral, and psychological factors on aging and age-related diseases is registered by the epigenetic modifications that can be used as "clocks".[111] As such, it is possible to determine the biological age and predict the life span and health span of an individual by using specific epigenetic biomarkers, called the epigenetic clocks. The first epigenetic clocks were developed in the early 2010s.[112,113] These first clocks were accurate in predicting the chronological age. Several clocks have been developed over the past decade.[111] The latest clock developed by Horvath, called GrimAge, is able to determine the epigenetic age acceleration by comparing the biological age with the chronological age.[114] GrimAge can thereby predict the life span of an individual, but it also provides information on risks of age-related conditions.[111] DNA methylation data have been found to accurately estimate the biological age for any tissue across the entire life course.[110] However, it could be preferred to use plasma cells because biological aging is associated with changes of the plasma proteome.[115] To the best of our knowledge, epigenetic clocks have not been determined in people with CHD to date.

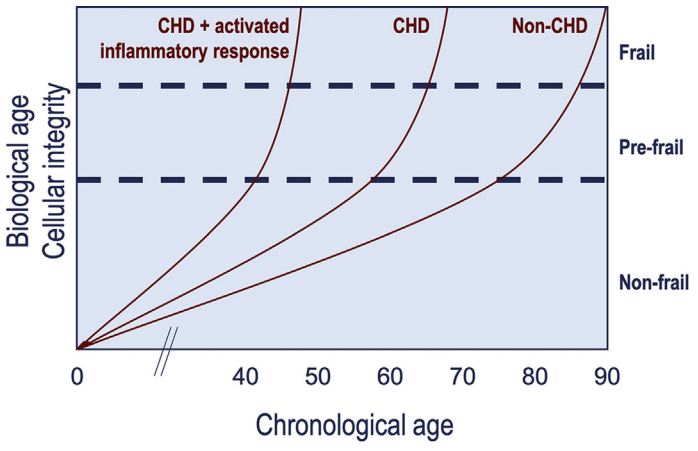
In summary, continuing to anchor the long-term outcomes in patients with CHD, on chronological age, facilitates standardization but is deceivingly simple. Indices of biological age, rate of aging, and integrative measures of aging well described in the geroscience literature have yielded very early yet bold applications in CHD with emerging data on frailty, sarcopenia, and telomere length in CHD. With advances in surgery, palliation, repair, and repeated interventions, it can be wondered if we have inadvertently generated an iatrogenic model of premature aging. Moreover, as we enter the second quarter on the 21st century, we need to question what the impact of accelerated inflammation with growing pandemic exposure to COVID-19 on our patient population might be.

THE IMPACT OF INFLAMMATION IN PATIENTS WITH CHD

The concept of "inflamm-aging" was introduced to capture the impact of an imbalance of inflammation homeostasis on aging.[116] Stress, oxidation-inflammation, cytokines, DNA damage, autophagy, and stem cell aging lead to dysregulation of the inflammatory response, contributing to accelerated aging. This results in abnormalities seen in a number of signaling pathways that lead to accelerated aging. Thus, accelerated aging can be seen as a chronic systemic inflammatory state with aging biomarkers that are markers of inflammation.[97]

Patients with CHD are found to have an activated inflammatory response,[117,118] especially those with cyanotic CHD[119] or after cardiac surgery.[120] Chronic inflammation in CHD is associated with the development of morbidities leading to frailty (**Figure 1**)[121] and yields a higher mortality.[122] Conditions we observe in our adult CHD population including

FIGURE 1 Inflamm-aging in CHD



Inspired by Franceschi C, Bonafè M, Valensin S et al. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann N Y Acad Sci*. 2000;908:244-254.[126]
CHD = congenital heart disease.

insulin resistance, atherosclerosis, and cancer have been attributed to "unresolved" inflammatory states.[116] A biomarker that is increasingly used in CHD is high-sensitivity C-reactive protein. In a study of 707 patients whose data were collected in the Boston ACHD Biobank from 2012 to 2016, high-sensitivity C-reactive protein was a significant predicter of adjusted all-cause mortality.[123] A novel biomarker of inflammation, however, is soluble urokinase plasminogen activator receptor (suPAR).[124] Elevated suPAR is found to be more sensitive to capture the impact of adverse childhood experiences, even more so than the proinflammatory biomarkers CRP and interleukin-6.[125] Given the life-course nature of CHD, suPAR appears to be a more appropriate biomarker in evaluations of aging in this population.

According to the Centers for Disease Control and Prevention in the U.S., patients younger than 30 years accounted for 20% of all COVID-19 cases and the number is steadily growing. One can thus wonder what the added effect of COVID-19 exposure might add to the already chronic or unresolved inflammatory state that patients with CHD have been shown to have. Thus, not surprisingly, in two studies in the U.S. and Europe, analyzing cases of COVID in patients with CHD, increased BMI, diabetes, cyanosis, pulmonary hypertension, and multisystem disease have been linked to adverse COVID outcomes.[127,128] The concept of inflamm-aging has been incorporated into an evolutionary perspective on immunosenescence.[126] This model can be adapted to CHD where acute inflammation superimposed on the chronic inflammatory condition associated with CHD can be seen as an effect modifier that will tip patients over the threshold of successful aging.

FUTURE RESEARCH DIRECTIONS

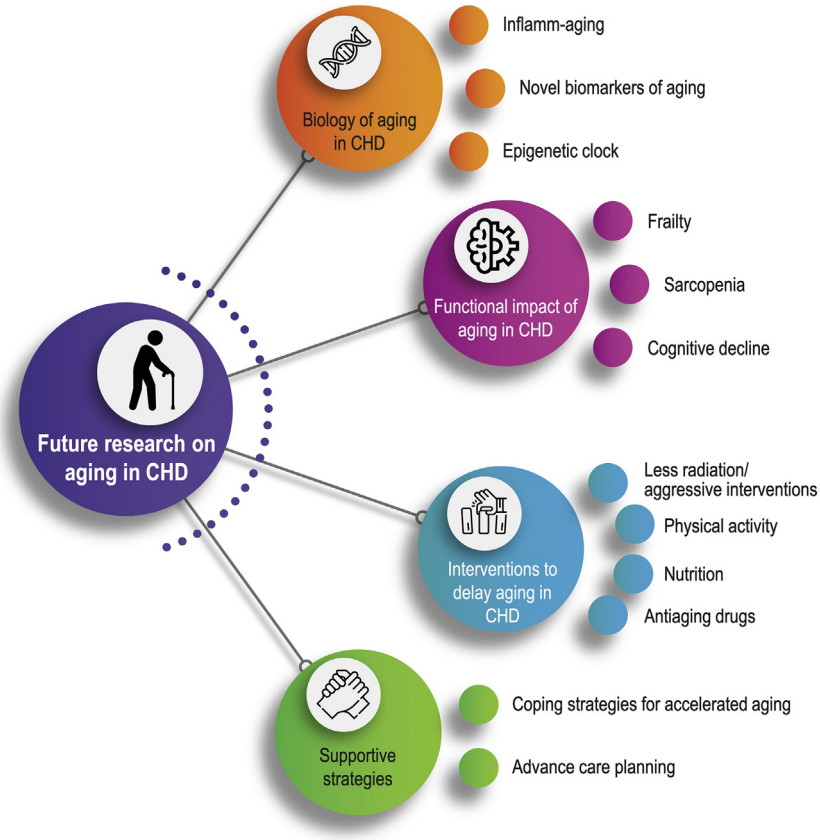
An in-depth investigation of novel biomarkers and the epigenetic clock could provide insights into the predictors and dynamics of aging across the course of life. These insights would pave the way to precision medicine in survivors of childhood-onset diseases, such as CHD. Indeed, when aging is investigated over the entire life course, and when physiological, psychological, and behavioral predictors of accelerated aging in CHD are identified, targeted interventions could be developed and implemented. Such interventions could slow down the accelerated aging process in afflicted patients in different stages of life. For instance, physical activity and nutrition are strategies that can be used for telomere maintenance.[129] Furthermore, epigenetic modifications are chemically reversible. Therefore, they can be targeted to reverse time and may be subject for rejuvenation strategies (**Figure 2**).[111] Nonetheless, the role of emerging antiaging drugs will need to be scrutinized for its use in CHD.

Irrespective of the efforts needed to better understand the aging process in CHD and to develop interventions to delay accelerated aging, it is also important to develop and test supportive strategies. For instance, health care professionals ought to support patients in coping with the accelerated aging. Hence, research agendas should include coping strategies with premature aging. To stretch this further, more research is needed on how to prepare patients with CHD earlier in life to cope with the inevitable. In this respect, effects of advance care planning ought to be investigated (**Figure 2**).

CONCLUSIONS

The population of patients with CHD is aging, as demonstrated by the changing demographics and the accumulation of cardiovascular and systemic complications. Concepts of aging have been developed in geroscience, and they are slowly finding their way to CHD. Functional markers of aging are frailty and sarcopenia. Biological markers are telomere length, epigenetic clock based on DNA methylation, and

FIGURE 2 Future Research Directions on Aging in CHD



CHD = congenital heart disease.

biomarkers of systemic inflammation. Evidence in this matter is sparse. To provide a new lens on aging in CHD and its functional consequences, this should be put high on the research agenda.

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