Review Article

Heart failure in the elderly – some aspects in pathophysiology, diagnosis and therapy that require special attention

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Abstract Approximately 50% of all heart failure patients in the US are above 75 years of age, which is almost similar to most European countries and the Middle and the Far East. Even though aging is an independent molecular process with a multitude of genetic pre-determination and biochemical mediations, aging itself does not automatically result in cardiac insufficiency. On the other hand, with increasing age, cardioprotective mechanisms in response to stress are lost, and progressive cardiomyocyte degeneration with replacement fibrosis is often seen in older hearts, even though the exact triggers are not completely understood. Older patients with heart failure have distinct features that require special attention in diagnosis as well as therapy. The elderly more frequently suffer from multiple co-morbidities and might have atypical clinical presentations. Several precautions are essential in the treatment of heart failure in the elderly due to co-existing morbidities and the pharmacokinetic and pharmacodynamic changes related to increased age. Also, treatment expectations, compliance, mental status and cognitive function might play a major role regarding optimized treatment and monitoring options in the elderly suffering from heart failure. This review summarizes current issues of heart failure management in the elderly. (J Geriatr Cardiol 2007;4:44-9.)

Key Words heart failure; aging; left ventricular function; mortality; elderly

"The secret of staying young is to live honestly, eat slowly, and lie about your age. " Lucille (Desiree) Ball, Television comedienne and film actress, 1911-1989

Introduction

The two entities that currently require major attention from a medical as well as an economic point of view are 1) the aging of the baby boomer generation, and 2) the increasing prevalence of heart failure. Obviously, there is a close connection between the two since heart failure was historically associated with the elderly. Furthermore, the elderly are those who have frequently suffered from "a weak heart". Approximately 5 million men and women suffer from heart failure in the US, and the worldwide prevalence is 1-2%. There are approximately 500,000 newly diagnosed cases of heart failure per year in the US. Interestingly, half of heart failure patients are older than 75 years of age, and heart failure represents the leading cause of death and of hospital admissions among the elderly. The German genius, poet, novelist and philosopher Johann Wolfgang von Goethe (1749-1832) stated that "Whoever, in middle age, attempts to realize the wishes and hopes of his early youth, invariably deceives himself. Each ten years of a man's life has its own fortunes, its own hopes, its own desires", and the American poet, editor and traveler Thomas Bailey Aldrich (1836-1907) added: "To keep the heart unwrinkled, to be hopeful, kindly, cheerful, reverent—that is to triumph over old age". Unfortunately, both of them very well realized that age has its common problems including those of worsening organ (cardiac) function. Interestingly, it is still unclear why and how exactly we do age, and why some do faster and other do slower, and what exactly determines or delays those processes of aging. As a young medical student I met the famous Hans Popper, chairman of pathology at Mount Sinai Hospital in New York and later president, and the father of modern hepatology when he was receiving his 14th honorary doctor title at the University of Goettingen in Germany. Dr. Popper himself at that time was above 90 years of age and presented data about aging. He stated that within the human body different organs age at different levels, so the liver is one of the few organs that does not age. Therefore, we are evaluating and using livers from patients in their 70s and 80s for transplantation. The reason for the preservation of hepatocellular structure (or the lack of aging) seems to be caused by the fact that the liver does not develop atherosclerosis and has an enormous regeneration...
capacity. This is in sharp contrast to the heart, which - next to the brain and the kidneys - is the most vulnerable organ for processes of aging. Cardiac tissue basically cannot regenerate lost tissue and exogenous stress, for example ischemia, can either result in acute cellular oncosis or in chronic conditions such as hibernating myocardium. In contrast to former conceptions, however, hibernating myocardium is not a stable equilibrium but represents progressive cardiomyocyte degeneration with loss of contractile material that results in replacement fibrosis. It is unclear, however, whether progressive aging automatically has to result in organ malfunction, i.e. in heart failure or whether heart failure - especially in younger people - is a result of (a premature) aging process. In order to try to shed some light onto the darkness of aging, this review discusses briefly the following topics: 1) the pathophysiology of cardiac aging, 2) diagnosis of heart failure in the elderly, and 3) treatment of heart failure in the elderly.

Pathophysiologic mechanisms of cardiac aging

Aging is associated with left ventricular hypertrophy, dilation of the cardiac chambers, and reduction of contractile material with subsequent replacement fibrosis. These structural changes are often associated with a reduction in function and other pathologic conditions. As demonstrated by echocardiography in a special set of high aged rats, Walker et al. showed left ventricle (LV) chamber dilation, increased wall thickness and a higher incidence of arrhythmias compared to young rats. Reexpression of the fatally expressed beta-myosin heavy chain (beta-MHC) gene is a well documented marker of pathological cardiac hypertrophy and normal aging in many experimental models and in aging heart, and it seems to be a marker of fibrosis (rather than of cellular hypertrophy).

Paternostro et al. have demonstrated in a drosophila model, that aged fruit-fly cardiac structure has a lower maximal heart rate in response to stress (ambient temperature and external electrical pacing) while arrhythmias increase compared to younger flies. In addition, the same drosophila model demonstrated an increase in electrical pacing-induced heart failure and arrhythmias in aging flies.

There are several more or less pre-determined processes in a cell's life that ultimately can result in either apoptosis (pre-determined cell death), cellular senescence, or malignant transformation. Several exogenous and endogenous factors seem to play a role in change of metabolic and cellular equilibrium. These factors are considered a stress. If stress causes damage of the cellular DNA, this results in a cellular response with induction of stress response proteomes by certain checkpoint proteins. It is the task of these checkpoint proteins to stimulate a signal transduction cascade that evaluate the present damage of the genome before repair mechanisms take place. If the repair mechanism fail, i.e., in the setting of malformation of checkpoint proteins or in overwhelming stress, tissue degeneration, premature and accelerated aging, and cancer transformation can occur. As known from studies in patients with ataxia teleangiectasia, abnormal DNA methylation can result in dysregulation of tissue specific epigenetic control over cell cycle checkpoints. Interestingly, this dysregulation has been shown to potentially result in degeneration such as calcification of aortic valves, atherosclerotic coronary artery disease, and heart failure in patients with diabetes mellitus. A recently published review focused on the “Disease Proteomics and Transcriptomics” that might serve as future diagnostic markers for these kinds of accelerated aging processes.

In particular in forms of heart failure secondary to diabetic cardiomyopathy, increased levels of O-linked attachment of N-acetyl-glucosamine (N-GlcNAc) on nucleocytoplasmic proteins have been shown to be implicated in the development of cardiac dysfunction. A recently published experimental study in rats demonstrated a significant increase in O-GlcNAc levels in high-molecular weight proteins in older diabetic rats compared to age-matched lean controls and compared to younger diabetic rats, which also was associated with impaired cardiomyocyte function, indicating that both diabetes as well as age alter the levels of O-GlcNAc expression and their regulatory function.

Moreover, the above mentioned drosophila model demonstrated that insulin receptors and associated pathways and altered ATP-dependent K channels change with age that seem to contribute to a reduction of cardioprotective mechanisms (for example, against ischemic-reperfusion injury) and also reduces cardiac performance.

Aging also has been associated with a selective up-regulation of transcripts involved in inflammation and oxidative stress, and a down-regulation of genes involved in mitochondrial electron transport and oxidative phosphorylation.

Another mediator that appears to contributes to preservation of structure and function in the heart is the serum response factor (SRF). SRF is increased in senescent and in heart failure. Interestingly, transgenic mice with lower levels of SRF were found to develop increased left ventricular wall thickness and decreased LV volumes, increased LV stiffness with 20% reduction in early diastolic LV filling, indicative of aging processes in human hearts. Maintenance of SRF levels without age-related increase - on the other hand - was associated with preserved LV systolic pressure and lower levels of brain natriuretic peptide in response to isoproterenol stimulation with higher mRNA levels of SERCA2 and ryanodine receptor 2 in transgenic mice. These findings suggested that preventing the age-associated increase in SRF might be associated with preserved intracellular calcium handling and stress response.

It has been suggested that changes at the level of the 'energy machines' within the cells, the mitochondria, deter-
mine processes of aging and cell death. Mutations in mitochondrial DNA such as base deletions or modifications are induced by oxygen-derived free radicals and are associated with aging and failing cardiac function. Mitochondrial alterations might result in impaired oxidative phosphorylation and defective electron transport chain activity that worsen further energy supply and creates more reactive oxygen species. Impaired respiratory chain function will then further augment free radical production and by thus, increase the rate of mitochondrial DNA mutation, which, in turn, will further compromise respiratory chain function, finally leading to cell death.\(^\text{13}\)

On the other hand, Trifunovic et al. proposed that premature aging phenotypes in mitochondrial DNA mutant mice are not generated by a vicious cycle of massively increased oxidative stress but that respiratory chain dysfunction itself induces premature aging in these animals.\(^\text{14}\) Still, the chicken and the egg have not been clearly defined in the cellular processes of aging.

**Diagnosis of heart failure in the elderly**

The diagnosis of heart failure in the elderly is much more difficult than it seems to be. This is caused by several factors such as atypical or difficult-to-interpret symptoms and a high frequency of co-morbidities that might mask or mimic symptoms of heart failure by concomitant presence of other diseases. Cognitive impairment, mental changes, neurological disorders and diseases of the musculoskeletal system also might contribute to the underutilized diagnosis of cardiac dysfunction and heart failure in this particular population. Heart failure in the elderly and very elderly differs in part substantially from heart failure among middle-aged adults: the proportion of women with heart failure is significantly higher, so is the proportion of diastolic dysfunction, which itself creates even more confusion in diagnostics and can easily result in inadequate therapy in view of preserved systolic LV function, as recently reviewed by Rich.\(^\text{15}\) Moreover, among older adults with heart failure, the proportion of older women with preserved LV function is also higher compared to men.\(^\text{16}\)

BNP testing has been shown to be very helpful to distinguish dyspnea of cardiac origin secondary to heart failure versus dyspnea caused by pulmonary or other causes such as chronic obstructive lung diseases, and thus, aids to diagnose and adjust treatment.\(^\text{17}\) In the elderly, however, there are few data available about the validity of BNP levels and the test is mainly used by cardiologists and emergency physicians but remains still widely underutilized among physicians taking care of geriatric patients. Moreover, changes of BNP levels in response to therapeutic unloading seem to be incoherent in the elderly.\(^\text{18}\)

Heart failure has been shown to be associated with impairment of cognitive function.\(^\text{19}\) In particular in the elderly, this oftentimes might be masked and remains unrecognized due to concomitant or pre-existing (mental) changes that are not related to the cardiovascular disorders and therefore, are not adequately addressed. More recently, an independent correlation has been found between the BNP levels and cognitive impairment associated with heart failure.\(^\text{20}\) In addition, Valle and co-workers showed the usefulness of discharge BNP levels as a predictor for post-discharge outcome in the elderly with decompensated heart failure.\(^\text{21}\) BNP to diagnose heart failure or to tailor therapy, however, seems to be underused among the elderly with vague and indeterminate symptoms.

Even though large scale data are lacking regarding the use of non-invasive and more invasive methods such as cardiac catheterization, early studies showed that diagnostic procedures decreased above ages of 75 years. The use of percutaneous transluminal angioplasty (PTCA) in patients with coronary artery disease decreased with increasing age, indicating that there is still continued ignorance or just lack of evidence-based knowledge about the efficacy of these tests and interventions in older adults.\(^\text{22}\)

Among additional investigations, even ultrasound remains underused, which is even more tragic since impairment of diastolic left ventricular function that hardly is determined by methods other than echocardiography.

Certain blood tests are helpful, in particular in view of drug accumulation risks, such as measurements of retention parameters (creatinine, blood urea nitrogen) and calculation of creatinine clearance.\(^\text{23}\) Due to oftentimes accompanied chronic renal insufficiency, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), loop diuretics and aldosterone antagonists have a higher risk of causing electrolyte imbalances and worsening of renal function, and therefore would require more frequent testing. While during hospitalizations due to decompensated heart failure this testing is frequently provided, after discharge and in nursing home settings it is not. Due to initial studies, home telemonitoring is useful for heart failure patients,\(^\text{24}\) but its clinical relevance and practical utilization needs to be more widely understood and executed in the elderly.

**Treatment of heart failure in the elderly**

The general objectives of treatment of heart failure in the elderly are alleviation of symptoms, improvement in the quality of life, reduction of mortality and the number and duration of hospitalizations, and slowing disease progression.\(^\text{23}\)

Compliance issues that are frequently caused by misconception, misunderstanding or forgetfulness need to be especially addressed in the elderly. Dietary recommendations and adherence to low salt or low fluid intake require more flexibility compared to those in younger patients, par-
particularly in order to prevent the risk of denutrition induced by strict salt-free diets. There are pharmacokinetic and pharmacodynamic changes related to aging. In addition, often a poly-pharmacy caused by multiple concomitant conditions requiring drug therapy might cause several drug interactions that even for health care providers can be outside the frame of their experience and knowledge. Drug elimination can be delayed caused by additional renal or hepatic dysfunction. Drugs dosage requires careful monitoring for adverse reactions. Education and involvement of care givers such as family members and written discharge instructions are essential in the care of the elderly with heart failure, ideally in the frame of a multidisciplinary team approach. Initial studies to optimize more frequent visits and/or monitoring in order to prevent re-hospitalizations and reduce costs have been either just presented or are on the horizon.

Data from several recent registries such as ADHERE revealed that we are far away from optimized and guideline-oriented heart failure therapy in the US due to underutilization of newer treatment recommendations. Other factors can influence and limit the use of drug regimen such as ACE inhibitors or ARBs in the presence orthostatic problems, the use of beta-blockers in the presence of dizziness or sexual dysfunction, the use of loop diuretics with the possible risk of dehydration secondary to reduced fluid intake. Anticoagulation that might be indicated to avoid thromboembolic complications in the presence of dilated ventricular chambers and/or atrial fibrillation poses additional risks in the elderly, in particular if there is a history of falls that can lead to potentially life-threatening hemorrhages.

Fortunately, invasive and more aggressive therapeutic procedures such as surgical revascularization procedures have increased in numbers in recent years in the elderly and even the very elderly. Obviously, in part this is secondary to a reduced surgical load due to more aggressive interventional procedures and the abundant use of PTCA and stents. Implantable defibrillators and biventricular pacers, however, are underutilized in the geriatric population. This in part is caused by misconception regarding the efficacy of left ventricular improvement, the relative low risk of the implantation procedure and the ability to turn the defibrillator off in cases of imminent death, both on the site of health care providers as well as patients. Heart transplantation as the ultima ratio therapy for end-stage heart failure was traditionally limited to a maximal recipient age of 65 years. This was mainly caused by the fact that in the early days of heart transplantation, patients above the age of 55 (considered as older patients) were found to be at higher risk for infection and other complications. Ten years ago, Richenbacher questioned whether heart transplantation should be offered to patients above 70 years of age. With more advanced techniques, immunosuppression with less organ toxicities and better monitoring capabilities, this is finally changing. We recently transplanted a 73-year-old patient and evaluated a 76-year-old for possible cardiac transplantation. Moreover, more multi-organ transplantations are performed just recently in older patients with multi-organ failure (for example, combined heart-liver-kidney transplantations). On the other hand, the updated guidelines for the management of heart failure in adults by the American Heart Association/American College of Cardiology published in September 2005 clearly recommend to include the option for hospice (palliative) care in the treatment regimen for patients (at all ages) with end-stage heart failure.

Besides drug and device therapy, exercise and diets have been shown to improve quality of life and reduce mortality and morbidity in heart failure patients. There is, however, no clear consensus regarding the optimal diet for heart failure patients, as recently reviewed by our group. Interestingly, in laboratory rodents, caloric restriction retards several age-dependent physiological and biochemical changes in skeletal muscle, including increased steady-state levels of oxidative damage to lipids, DNA, and proteins. A diet low in calories appeared to prevent or delay most of the major age-related transcriptional alterations in the gastrocnemius muscle of C57BL/6 mice. However, in a study in rhesus monkeys the authors did not find evidence for an inhibitory effect of adult-onset calorice restriction on age-related changes in gene expression. Just very recently Halton et al. presented almost similar data in humans, showing that a low carbohydrate diet may reduce the coronary artery disease risk in women.

Exercise training has been repeatedly shown to improve conditioning, cardiac performance and symptoms in patients with heart failure. In the elderly, concomitant diseases such as arthrosis and arthritis, loss of vision and hearing among several other features might limit exercise capabilities. However, regular exercise has been shown to benefit elderly patients with heart failure, too, and thus, all efforts should be undertaken to enroll elderly heart failure patients in regular exercise programs.

Data in the older patient population with heart failure are rare. This in part is caused by the fact that most of our clinical trials in heart failure exclude the group of patients that we are dealing with most, such as the elderly, women, and patients with diabetes and chronic renal insufficiency, since age above 75 years and concomitant diseases are often exclusion criteria. This has been recently demonstrated by data from huge registries such as the ADHERE registry (>150,000 patients) that represent more real-life scenarios and populations than those in randomized clinical trials.

Conclusions

We are in fact so virgin and ignorant in the field of geriatric cardiology, that we oftentimes – as in this article – summarize the elderly as one conglomerate. With further knowledge of the processes of aging and better care of the
elderly, we might need to distinguish between numerical and biological age and between different age groups. Today’s 70 year olds are like 50 year olds 20 years ago, and today many octogenarians are biologically like in their 60s a while ago. In order to specify more detailed individual problems in the elderly we might have to consider septuagenarians as being different from octogenarians. Different socio-cultural influences and experiences create different expectations on quality of life. In particular since life span and survival has changed due to advanced technologies and therapies, the elderly not only have special needs but also rights regarding quality of life. Adequate treatment of sexual dysfunction in patients at high ages - in particular in those with heart failure – is still a new field we are exploring in research as well as in clinical practice but has huge success potential many health care providers as well as patients are not aware of and thus, deserves more attention. Community activities and measures such as optimized wheelchair access among several other medical and nursing care aspects also have a huge impact on quality of life in the elderly.

Altogether, we are in urgent need of more intense dedicated basic research on processes of aging, in particular of the heart and the blood vessels, as well as clinical research to study the effects of aging and requirements for age-adjusted therapies as well as special care for those among us above the middle age. Until then, we might just as well follow the below quotation of the Swiss author Karl Viktor von Bonstetten (1745-1832), who has been called a writer of wide cosmopolitan interests and outlook:

"To resist the frigidity of old age one must combine the body, the mind and the heart - and to keep them in parallel vigor one must exercise, study and love".

References


