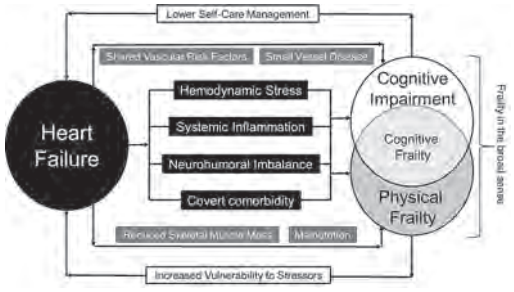
Heart and Metabolism

Number 76 - July 2018



The frail patient with heart disease: please handle with care!

76

HEART AND METABOLISM

Heart and Metabolism a Servier publication

Published by Les Laboratoires Servier

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Aim and Scope *Heart and Metabolism* is a journal published three times a year, focusing on the management of cardiovascular diseases. Its aim is to inform cardiologists and other specialists about the newest findings on the role of metabolism in cardiac disease and to explore their potential clinical implications.
Each issue includes an editorial, followed by articles on a key topic. Experts in the field explain the metabolic consequences of cardiac disease and the multiple potential targets for pharmacotherapy in ischemic and nonischemic heart disease.

Website www.heartandmetabolism.com

Heart and Metabolism is indexed in EMBASE, SCOPUS, and PASCAL/INIST-CNRS.

Design Studio DTC - Servier
Layout Bleu Banquise

Printed in France

ISSN 1566-0338

PEFC 00-00-0000 / PEFC Certified / This publication is from sustainably managed forests and controlled sources. / www.pefc.org

Mini-Mental Status Examination (MMSE)

The MMSE is a screening instrument/questionnaire used to assess mental status by testing five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score is 30, while a score of 23 or less is indicative of cognitive impairment.

Montreal Cognitive Assessment (MoCA)

The MoCA is a screening instrument designed to detect mild cognitive impairment in patients scoring in the normal range of the MMSE. Multiple cognitive domains are assessed with the MoCA, including short-term memory; visuospatial abilities; executive function; attention, concentration, and working memory; language; and orientation to time and place. A clinical cut-off score of 26 is indicative of mild cognitive impairment.

Sarcopenia

Sarcopenia is a condition involving a degenerative loss of skeletal muscle mass of ≈0.5% to 1% per year (once an individual reaches 50 years of age). It is therefore characterized by muscle atrophy in addition to a reduction in muscle tissue quality. Sarcopenia is frequently associated with both cachexia and frailty syndrome.

Society of Thoracic Surgeons score

The STS score is an American risk score toolset (the European equivalent is the EuroSCORE) used to predict operative mortality of adult cardiac surgery within 30 days of the operation or later if the patient remains hospitalized.

Transcatheter aortic valve implantation

TAVI is a surgical procedure that involves a small incision in the chest, following which a catheter is inserted through the groin into a large blood vessel for implanting an aortic valve (usually made of natural tissue from either a cow or a pig) over an individual's existing aortic valve. The catheter is removed once the new valve is implanted and will start working immediately.

Contents

Heart Metab. (2018) 76:2-3

The frail patient with heart disease: please handle with care!

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Improvements in life expectancy in our aging society have resulted in an increased prevalence of frailty in patients with ischemic heart disease (IHD), heart failure (HF), and cardiac valve disease. Frailty, which has been defined as a state of increased vulnerability to external stressors and decreased physiological reserve, has important implications on the management of these conditions in elderly patients – in particular, its' presence is known to be predictive of worse clinical outcomes. In this issue of *Heart and Metabolism*, strategies for improving the detection and management of frail patients with cardiovascular disease (CVD) are discussed.

In the opening article, Dr Nicola Veronese explores the challenges facing the detection and management of the frail patient with CVD. The close interplay between frailty and CVD is highlighted, with frailty being a risk factor for developing CVD and vice versa. This can be explained in part by the shared etiological factors between these two conditions, including low-grade inflammation, cellular senescence, and endocrine dysregulation, among others. In the next article, Dr Ken Shinmura explores the triangular relationship between frailty, HF, and cognitive impairment. In at least one-quarter of elderly patients, HF is complicated by both physical frailty and cognitive impairment. The pathophysiology underlying HF directly contributes to frailty by reducing exercise capacity and skeletal muscle function. Furthermore, patients with HF are more susceptible to cognitive impairment, which accelerates the development of physical frailty and HF, resulting in a vicious cycle. Crucially, there are no standardized screening tools for cognitive impairment in patients with HF, and there is an incomplete understanding of the complex relationships between frailty, HF, and cognitive impairment. Strategies that increase cardiac output, such as exercise have been shown to increase cognitive function and may be used as a therapeutic intervention in frail patients with HF.

Transcatheter aortic valve implantation (TAVI) is an increasingly common intervention for older patients with aortic stenosis who are at risk of complications from major cardiac surgery. The challenge has been to have objective and reproducible physical frailty measures that can be used to identify patients at the very highest risk of early mortality or worsening disability after TAVI. In their article, Drs Atul Anand and Nicholas L. Mills, discuss several frailty measures that may be used to help assess risk in older patients with aortic stenosis and guide patient selection for TAVI in order to maximize the benefit of treatment. In the following article, Drs Li Ying Koh and Nian Chih Hwang provide an anesthetists' perspective on managing frail patients with coronary artery disease undergoing cardiac surgery who are at risk of experiencing worse clinical outcomes postsurgery. Conventional preoperative risk scores do not take into account the increased physiological vulnerability of the frail patient; therefore, frailty-specific risk scores are needed

to improve preoperative risk assessment in this setting. The issue of cardiovascular pharmacotherapy in frail patients with IHD is addressed in the article by Drs Cristiana Vitale, Massimo Fini, and Giuseppe Rosano. Certain cardiovascular drugs are known to impair quality of life and functional capacity in frail patients with CVD. In this regard, β-blockers are associated with an increased risk of cognitive decline and a reduced ability to independently perform activities of daily living, and ivabradine, which is well tolerated in frail elderly patients, may provide an alternative therapy. Conversely, drugs known to have a positive effect on functional capacity and quality of life in frails patients can be considered. For example, the antianginal agent trimetazidine has been shown to improve myocardial ischemia, exercise capacity, quality of life, and prognosis in elderly patients.

Frailty has been associated with worse clinical outcomes following acute coronary syndrome and PCI. Therefore, frailty status should be taken into careful consideration when treatment strategies are planned. In this issue's case report, Dr Luciano Candilio describes the case of an 87-year-old patient undergoing PCI for non–ST-segment elevation myocardial infarction and evidence of multivessel coronary artery disease, who had significant comorbidities, including chronic kidney impairment, peripheral artery disease, and chronic obstructive pulmonary disease. His frailty status was carefully evaluated and the risks and benefits of potential management strategies were taken into account by his heart team. He underwent a successful staged PCI to his left main stem and right coronary artery with chronic total occlusion, and he reported no symptoms on a subsequent follow-up and a significantly improved quality of life.

In the refresher corner, Dr Gary D. Lopaschuk reviews the changes in cardiac metabolism in the aged heart, and, subsequently, how these alterations in energy production can compromise the ability of the heart to adapt to stresses requiring an increase in energy demand. Therefore, improving both cardiac energy production and the efficiency of energy production may be a novel therapeutic strategy to lessen cardiac disease in the elderly.

Finally, in the hot topics article, Drs Shane Nanayakkara and David M. Kaye review the role of diet and exercise as potential strategies for improving health outcomes in frail patients with CVD. In HF patients with frailty, it has been shown that exercise reduces rehospitalization rates, improves quality of life, and is a cost-effective intervention. Although frailty and nutritional status are closely linked, the evidence for dietary modification, such as increased protein intake or vitamin supplementation, has produced mixed results. Further studies are needed to investigate the efficacy of therapeutic strategies for improving health outcomes in frail patients with CVD.

In summary, this issue of Heart and Metabolism highlights the challenges in detecting and managing frail patients with IHD, HF, and cardiac valve disease. Much more work is needed to improve frailty-specific risk assessment so management can be personalized to aged patients in order to improve health outcomes in this increasingly important patient group. ■

Heart Metab. (2018) 76:4-7

The frail patient with heart disease: an emerging and challenging issue

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Abstract

Frailty and cardiovascular disease (CVD) are two common conditions that may affect clinical outcomes in older people. Epidemiological studies suggest that CVD is one of the most important contributor to the development of frailty in the aged patient, and the latter can therefore be considered a potential CVD risk factor. Moreover, traditional CVD risk factors are also known to be important for developing frailty. This close relationship between CVD and frailty is due, in part, to the shared etiological factors, which include low-grade inflammation, cellular senescence, and endocrine dysregulation. Therefore, the early detection of frailty is important in the management of patients with CVD or in those who are at a high risk of developing CVD. In this regard, the use of a comprehensive geriatric assessment (CGA) may be considered in these patients. Unfortunately, the literature available for the use of CGA is only based on observational data, which may be biased; therefore, future studies are needed to understand the true role of CGA for detecting frailty in patients with CVD. In this article, an overview is provided of the current evidence regarding frailty, CVD, and their coexistence in terms of the underlying pathophysiology and their impact on clinical outcomes. ■ *Heart Metab*. 2018;76:4-7

Keywords: cardiovascular disease; comprehensive geriatric assessment; frailty

Introduction

Frailty has been traditionally defined as "reduced physiological reserve and increased vulnerability for poor resolution of homeostasis after a stressor event."[1] It is a common condition in older people, affecting about one person in ten.[2] The prevalence of frailty in people affected by cardiovascular disease (CVD) is higher than in those without CVD,[3] but increasing numbers of studies suggest that the relationship between frailty and CVD is closely intertwined, ie, frail people are at an increased risk of CVD and vice versa.[4] Finally, the presence of frailty in patients with CVD (and vice versa) appears to have important prognostic implications.[5] This article provides an overview of the current evidence regarding frailty, CVD, and their coexistence in terms of the underlying pathophysiology and their impact on clinical outcomes.

Epidemiological research regarding frailty and CVD

From an epidemiological point of view, frailty and CVD are strongly associated. Traditional CVD risk

Abbreviations

CGA: comprehensive geriatric assessment; **CVD:** cardiovascular disease

factors, namely diabetes, obesity, and a sedentary lifestyle, appear to be risk factors for developing frailty.[6-8] Moreover, it has been reported that subclinical CVD parameters (eg, the presence of atherosclerotic plaques and higher carotid intima media thickness) are more commonly observed in frail subjects when compared with nonfrail patients.[9] Finally, recent literature has shown that CVD is one of the strongest risk factors for developing frailty[4] and that the presence of frailty can increase the risk of developing CVD.[10,11] When frailty coexists with CVD, the clinical implications for older people are more impactful with clinical importance. Frailty has been associated with increased morbidity, mortality, and disability in patients affected by CVD undergoing cardiac or noncardiac procedures, although most of the research data have been limited by studies using small sample sizes and by a lack of randomized trials.[12]

Common pathophysiology underlying CVD and frailty

From a pathophysiological point of view, it has been reported that there are many molecular and cellular pathways in common between frailty and CVD *(Figure 1)*. First, low-grade inflammation is more common

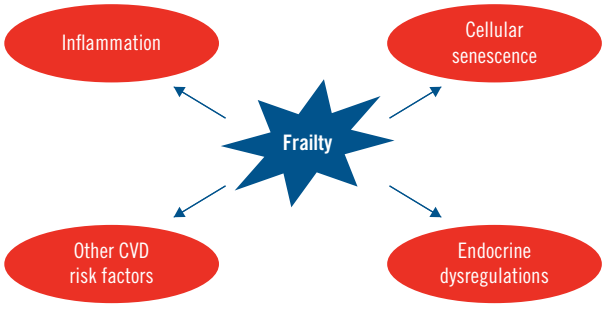

Fig. 1 *Pathophysiological associations between frailty and cardiovascular disease.*

in frail older patients when compared with less frail older patients,[13] and low-grade inflammation is well-established to play a major role in the development of CVD.[14] Second, frail patients are known to have cellular and intracellular alterations typical of cellular senescence (eg, marked DNA damage[15] and shorter telomere length),[16] the presence of which may contribute to the development of CVD. Third, endocrine dysregulation that is present in frail patients (eg, lower insulin-like growth factor (IGF)-1 levels)[17] can further increase the risk of CVD in patients affected by frailty. An important role may be played by insulin resistance, a key factor for developing CVD, which is more prevalent in frail patients than in less frail patients.[18]

Importance of frailty in the management of older people with CVD

The topic of frailty in the context of CVD is of increasing importance to both geriatric medicine and cardiology. Appropriate and early intervention may help prevent the development of frailty in patients with CVD.[19] Examples of these interventions include physical exercise (particularly resistance training), nutrition, cognitive training, and medication review.[20]

Since frailty is traditionally defined by physical performance items, particular importance is given to physical exercise. Exercise seems to have a positive effect on various measures used to determine frailty (eg, cognition, physical functioning, and psychological well-being) and some studies revealed that exercise may prevent or, at least, delay the onset of frailty.[21] However, we do not know which type of physical exercise is best for preventing and treating frailty, since it is estimated that aerobic endurance training can improve peak oxygen consumption, but resistance training is the best way to increase muscle strength and mass.[22] Probably, a combined intervention (both aerobic and resistance training) is the best way to treat frailty successfully.[22]

Diet is the other intervention for treating frailty. Most studies have shown that dietary supplements or improvements in dietary intake can improve factors related to frailty, such as muscle strength, walking speed in frail or prefrail older adults.[23] However, nutritional interventions are probably not sufficient for treating/preventing frailty without physical exercise.[24]

Several interventions used for treating frailty are useful for reducing CVD risk[25] and specific interventions, such as a heart transplant, are useful for reversing frailty.[26] Finally, frailty, particularly in its initial stages, can represent a window for appropriate interventions, specifically lifestyle interventions, that may delay the onset of CVD and consequently reduce disability, hospitalization, and mortality.[27]

Heart Metab. (2018) 76:4-7

Comprehensive geriatric assessment in patients with CVD

An increasing body of literature supports the importance of a comprehensive geriatric assessment (CGA) in the management of medical conditions common in older individuals, eg, hip fractures.[28] Therefore, it is likely that older patients with CVD may also benefit from a global and multidimensional geriatric approach. The literature regarding this topic, which is limited to a few studies,[29] has shown that older adults with low CGA scores had worse short- and long-term prognoses.[29] To the best of our knowledge, only observational studies are available, and, although they can provide important information, they may suffer from some biases. Moreover, these studies explored only mortality as an outcome, whereas other parameters of clinical importance, such as quality of life, were not included.[29] CGA could be useful in the management of CVD for several reasons, particularly because interventions to prevent frailty may break the vicious cycle between frailty and CVD, which would improve global physiological reserve and consequently outcomes.[30]

Recent guidelines recommend the early recognition of frailty in older patients to provide an estimate of prognosis and to avoid potentially ineffective and expensive medical interventions.[31] For example, the European Society of Hypertension and the European Union Geriatric Medicine Society Working Group on the management of hypertension have suggested that, for frail subjects, therapeutic decisions should be preceded by: (i) obtaining accurate information on functional capacity and cognitive status; (ii) paying attention to multiple drug administration; (iii) stratifying the frailty status using one of the available rapid methods; and (iv) identifying and correcting factors or conditions that predispose patients to common and possibly severe adverse treatment effects.[32]

Therefore, the clinical approach to older patients affected by CVD cannot be limited to a traditional, purely cardiological paradigm, but should also consider the peculiarities of these syndromes, which also include common issues in the physical, psychosocial, and cognitive domains. Complex clinical pictures and highly unstable health trajectories distinguish older ill adults, for whom a traditional clinical approach that is only based on disease-specific guidelines can be misleading with regard to prognosis, resulting in poor quality of care and negative outcomes.[33] In this regard, physical performance assessment contributes to functional evaluation and provides important prognostic information in older patients affected by CVD.

Future directions

The research of the potential relationship between frailty and CVD is intriguing, but unfortunately, it is only based on observational data. A summary of the most important concepts are provide here:

- Frail patients with no clinical evidence of CVD: lifestyle interventions (eg, physical exercise, nutritional interventions) might reduce the onset of CVD compared with standard care. The use of other common primary prevention interventions, such as low-dose aspirin, is still debated.[34]
- Frail patients with CVD: many of the interventions that can be used for reversing frailty are probably useful for improving CVD outcomes, but more interventional research is needed.
- Role of CGA: an integrated model of care, as has been developed for orthogeriatrics, is probably the best approach to understand the role of a geriatrician in the treatment of frailty in patients affected by CVD and vice versa.

Conclusions

Frailty and CVD are two common conditions in older people. Increasing literature reports demonstrate an important interdependence between the presence of frailty and CVD. Interventional studies are needed to obtain a better understanding of the role of treating frailty to prevent CVD. ■

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Heart Metab. (2018) 76:8-12

Frailty, heart failure, and cognitive impairment: a triangle in elderly people

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Abstract

Considering the high incidence of heart failure (HF) in elderly individuals, more attention should be given to geriatric conditions, especially frailty and cognitive impairment. These conditions significantly affect the course of HF, its management, and its prognosis in the elderly. The recently developed concept of frailty includes both the decline in physical function and cognition. The prevalence of physical frailty and cognitive impairment ranges between 15% and 74% and between 25% and 80%, respectively, depending on the criteria used for the diagnosis and on the study population. It is estimated that, in at least one-quarter of elderly patients, HF is complicated with both physical frailty and cognitive impairment. To date, there are no standardized screening tools for cognitive impairment in patients with HF, but the Montreal Cognitive Assessment seems to be better than the Mini-Mental Status Examination. The mechanistic relationships between HF and cognitive impairment are complex and have not been fully elucidated. One of the most important factors is cerebral perfusion abnormalities in patients with HF; therefore, specific interventions that can increase cardiac output may improve cognitive impairment in patients with HF. Increasing evidence demonstrates that cognitive function significantly improves following, among other possible treatments, exercise in patients with HF. Further investigations regarding the pathophysiological interaction among physical frailty, HF, and cognitive impairment are needed to implement strategies to treat or prevent frailty in elderly patients with HF. ■ *Heart Metab*. 2018;76:8-12

Keywords: cognitive impairment; elderly; physical frailty

Elderly patients with heart failure: high risk for frailty and cognitive impairment

Along with the robust increase in the elderly population, the increasing incidence of heart failure (HF) in older people has become the most challenging problem in developed countries due to the associated high mortality rates and economic costs.[1,2] Considering the advanced age of individuals with HF, we should pay more attention to geriatric conditions, including multiple morbidities, polypharmacy, disability, malnutrition, frailty, and cognitive impairment.[1,3-5] Each of these conditions significantly affects the course of HF, its management, and its prognosis in the elderly.

Abbreviations

ADL: activities of daily living; **CBF:** cerebral blood flow; **HF:** heart failure; **IADL:** instrumental ADL; **LVAD:** left ventricular assist device; **MMSE:** Mini-Mental Status Examination; **MoCA:** Montreal Cognitive Assessment

Frailty represents a complex clinical syndrome characterized by decreased physiological reserve, increased vulnerability to stressors, and most importantly, reversibility by appropriate interventions.[2-5] Frailty was mainly considered from the perspective of decline in physical function, the so-called physical frailty. Recently, neuropsychiatric status, including cognitive impairment and depression, as well as social conditions, such as solitude, have been shown to contribute to frailty.[5,6] A consensus group consisting of the International Academy on Nutrition and Aging and the International Association of Gerontology and Geriatrics defined cognitive frailty as "a syndrome in older adults with evidence of both physical frailty and cognitive impairment without a clinical diagnosis of Alzheimer's disease or another dementia."[7]

Among patients with HF, the prevalence of frailty ranged from 15% to 74%, depending on the criteria used for diagnosis and on the study population.[3,5] The pathophysiology of HF directly contributes to frailty by reducing exercise capacity and skeletal muscle function. Furthermore, patients with HF are more susceptible to cognitive impairment, which accelerates the development of physical frailty and HF, resulting in a vicious cycle.[1-4]

This review discusses the pathophysiology and clinical implications of and therapeutic strategies for cognitive impairment in elderly patients with HF.

Definitions, assessment, and epidemiology

Cognition is a superior cortical function involving multiple brain processes that allow an individual to perceive information, learn, and remember specific knowledge and use this to solve problems and plan actions in daily life.[8,9] Cognitive function covers different specific aspects, known as cognitive domains, including memory, attention/working memory, psychomotor speed, executive function, language/speech, and visuospatial/constructional function.[8,9]

Cognitive impairment in elderly patients with HF indicates impairment of one or more of the above-mentioned cognitive domains, and presents acutely as delirium or chronically as dementia or mild cognitive impairment.[2,3,10] Dementia is a chronic condition characterized by severe cognitive impairment that interferes with an individual's ability to perform basic activities of daily living (ADL) and instrumental ADL (IADL), social activities, and occupational responsibilities. Dementia is progressive and generally irreversible. In contrast, mild cognitive impairment is defined as chronic cognitive deficits that make any performance of IADL more difficult than usual, but which are not severe enough to impair the ability to perform most IADL and basic ADL. Despite the observed constant rate of mild cognitive impairment progressing to dementia, mild cognitive impairment is thought to be a reversible condition, similar to physical frailty.[2,3,6,10]

The prevalence of cognitive impairment in patients with HF ranged from 25% to 80%, depending on the measures used and the characteristics of the HF sample studied.[4,9-15] Patients with HF have a higher risk for cognitive impairment than people without HF, after controlling for other factors, such as age, sex, and comorbidities.[16] In patients of similar age with or without HF, patients with HF had worse cognition in the domains of memory, attention, psychomotor speed, and executive function.[8,9] In contrast, language and visuospatial ability are less affected in patients with HF, although only a few studies assessed them in patients with HF. Interestingly, Athilingam et al showed that the pattern of impaired cognitive domains was different between patients with HF with reduced ejection fraction and patients with HF with preserved ejection fraction.[17] This finding might be associated with the pathophysiology of cognitive impairment in patients with HF.

Despite the higher prevalence of cognitive impairment, there are no standardized tools recommended to screen for cognitive impairment in patients with HF. The Mini-Mental State Examination (MMSE) is a widely used instrument for cognitive testing in older people, with or without HF[10,11,13,18]; however, it seems to lack sensitivity for detecting mild cognitive impairment.[10,11,18] Patients with HF and mild cognitive impairment will often score within the normal range on the MMSE, meaning that mild cognitive impairment may be underestimated. A recent study demonstrated that the observed prevalence of cognitive impairment by the MMSE score corrected by age and

Heart Metab. (2018) 76:8-12

education were 27.6% in patients with HF (mean age, 71±11 years).[13] The Montreal Cognitive Assessment (MoCA) is being increasingly used in patients with HF because the MoCA covers numerous cognitive domains and is sensitive for detecting cognitive deficits in older patients with HF.[9-12,18] A recent study demonstrated that physical frailty was identified in 49% of patients with HF and that 58% of them had cognitive impairment detected by the MoCA.[12] In contrast, the complication of cognitive impairment in nonfrail patients with HF was only 8%, although the mean age of the sample in this study was 57±10 years. Therefore, it is expected that at least one-quarter of patients with HF are suffering from cognitive frailty. A recent systematic review and meta-analysis indicated that the odds ratio for cognitive impairment in the HF population was 1.67 (95% CI, 1.15-2.42) in case control studies involving those with and without HF (1414 participants).[16] This study also revealed that the prevalence of cognitive impairment in HF cohorts (4175 participants) was 43% (95% CI, 30-55).

Pathophysiology

The mechanistic relationships between HF and cognitive impairment are complex and not fully elucidated; however, there are several emerging themes within the literature that provide mechanistic insight into this relationship *(Figure 1)*.[2,3,6,9,11,19] Risk factors are independently associated with both HF and cognitive impairment.[2,3,6] For example, coronary artery disease, hypertension, and diabetes mellitus are independent risk factors for cognitive impairment, which is also frequently observed in patients with HF. In addition, depression, atrial fibrillation, and sleep apnea are more common in patients with HF than in the general population, and each of these conditions is independently associated with cognitive impairment.[2,3,6]

One of the most important factors for cognitive impairment is hemodynamic stress in patients with HF.[2,9,19] Reduction in cerebral blood flow (CBF) is often considered a determinant in brain changes affecting patients with HF. CBF depends on several variables, such as cardiac output, blood pressure, and cerebrovascular reactivity.[9] Cerebral microvascular architecture in older patients is disrupted by a combination of age-associated changes and vascular risk factors.[2] Therefore, it is difficult to maintain adequate CBF in response to hemodynamic disturbances. The capacity of cerebral vascular autoregulation is further reduced in older patients with HF. In addition, disruption in cerebral perfusion may result from abnormal blood viscosity that contributes to the development of microemboli in patients with HF.[2,19] Cardiac output is an important determinant of CBF.[9,19] Evidence from large observational studies showed that reduced cardiac output is linked to cognitive impairment.[9,19] A recent study by Suzuki et al demonstrated that reduced CBF in the posterior hippocampus was significantly associated with the severity of cognitive impairment in patients with HF.[20] The posterior hippocampus plays a major role in cognitive function and its hypoxic vulnerability has been confirmed in patients being resuscitated after cardiac arrest.[20]

In addition to hemodynamic stress and hypercoagulation in patients with HF, systemic inflammation may contribute to the development of cognitive impairment by inducing neuroinflammation and disrupting neurovascular coupling in the blood-brain barrier.[6,11,19] The coexistence of systemic inflammation is also associated with the development of physical frailty in patients with HF.[5] Furthermore, the changes in the neurohormonal axis of patients with HF may have a role in the relationship between HF, cognitive impairment, and structural brain changes,[6,11] includ-

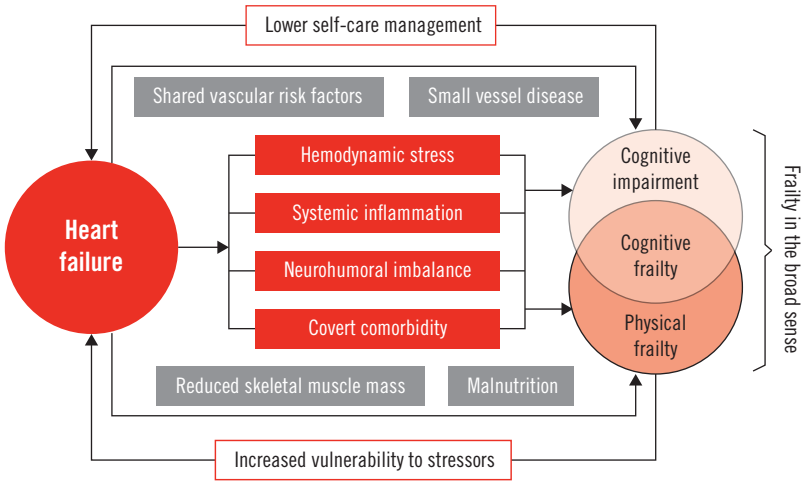

Fig. 1 *Pathophysiology and the impact between heart failure, cognitive impairment, and frailty.*

ing elevated serum levels of cortisol and catecholamines and activation of the renin-angiotensin-aldosterone system.

Clinical impact and therapeutic strategies

Cognitive impairment can affect the ability of elderly patients with HF to manage their disease, recognize worsening of symptoms, make appropriate decisions about their health, and adhere to specific and complex therapeutic regimens, meaning that they have a significantly lower self-care management.[9,10] The coexistence of cognitive impairment in patients with HF is very important in determining mortality, hospital admission, poor quality of life, and functional decline.[1-3] At worst, patients with HF and cognitive impairment exhibited almost a five-fold increase in mortality.[15]

The course of cognitive changes in patients with HF was examined in the context of HF treatments and the length of follow-up periods vs a control group.[14] Hajduk et al reported that a significant decline in cognitive function was observed in patients with HF followed-up after more than 1 year.[14] In contrast, cognitive function in patients with HF improved over a short time period (<1 year) when they underwent interventions to ameliorate cardiac function. In the studies using a comparison group without HF, cognitive function in patients with HF decreased or stabilized over time, suggesting that patients with HF are at risk for cognitive decline, but this risk seems to be modified by appropriate cardiac treatment.

While cognitive function improved after cardiac transplantation and following left ventricular assist device (LVAD) implantation,[21,22] recent studies showed that LVAD implantation did not improve cognitive function significantly, although it improved the frailty status.[23,24] Cardiac resynchronization therapy is reported to not only improve cardiac function, but also cognitive function in selected patients with symptomatic HF.[25,26] These interventions might improve cardiac output and reduce cerebral hypoperfusion, but are not applicable in all patients with HF.

Other possible treatments include exercise, increasing physical activity, and treatment for comorbidities, such as hypothyroidism, vitamin B12 deficiency, sleep apnea, anticholinergic medication use, depression, infections, and visual and hearing disturbances.[2,9-11] Taking measures to minimize polypharmacy and malnutrition in patients with HF are useful to prevent cognitive decline.[1,2] Treatment with angiotensin-converting enzyme inhibitors[27] or digoxin[28] may improve neuropsychological functions. Increasing evidence demonstrates that cognitive function significantly improves following exercise in patients with HF.[2,11,29,30] Exercise and cardiac rehabilitation are also effective to prevent the development of physical frailty.[1,5]

Unfortunately, no definitive consensus on the optimal method to avoid changes in cognitive function in patients with HF has been achieved. Further investigations regarding the pathophysiological interactions among physical frailty, HF, and cognitive impairment are needed to identify strategies to treat or prevent cognitive impairment in elderly patients with HF. ■

Funding sources: *This study was supported by the JSPS KAKENHI (Grant Number 16KT0012) (2016-2018) and by the Vehicle Racing Commemorative Foundation (2017-2018).*
Disclosures: *The author declares no conflicts of interest.*

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Heart Metab. (2018) 76:13-17

Aortic stenosis in the frail patient: maximizing the benefit of TAVI

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Abstract

Transcatheter aortic valve implantation (TAVI) is an increasingly common intervention for older patients with aortic stenosis deemed at high risk of complications from major cardiac surgery, but identifying those who will benefit can be challenging. Frailty, as a measure of physiological reserve, may be a useful prognostic marker in this population. In this brief review, we summarize the frailty tools that have been studied in TAVI cohorts and the reported outcomes for these patients. Frailty is associated with poorer outcomes after TAVI and assessment provides information beyond conventional surgical risk calculators, such as from the Society of Thoracic Surgeons (STS) and EuroSCORE. Of more use to the clinician is understanding that objective and reproducible physical frailty measures can identify patients at the very highest risk of early mortality or worsening disability after TAVI. Using these tools to help assess risk in older patients with aortic stenosis and guide patient selection for TAVI has great potential to maximize the benefit of treatment. ■

Heart Metab. 2018;76:13-17

Keywords: aortic stenosis; frailty; TAVI

Introduction

Transcatheter aortic valve implantation (TAVI) has opened the possibility of definitive treatment of aortic stenosis to a wider population of increasingly older and frailer patients. As the most common valvular disease in the Western World, rates of severe symptomatic aortic stenosis are rising as the population ages.[1] Increasingly, these patients have greater comorbidities and are considered at an excessive risk of death or complications from conventional surgical valve replacement. The PARTNER randomized controlled trial (Placement of AoRtic TraNscathetER valves) on TAVI vs medical management demonstrated a 45% reduction in the 12-month mortality with an intervention.[2] However, medical complexity continues to challenge decision-making in this area; among those who received TAVI in the PARTNER trial, nearly one-third had died within 12 months and a small, but significant, number experienced periprocedural strokes or major vascular complications. Uncertainty remains for many older individuals presenting with symptomatic severe aortic stenosis and multimorbidity. Increasingly, this risk calculation is framed by frailty, in an acknowledgement that current surgical tools, such as the Society of Thoracic Surgeons (STS) score, do not accurately represent the risk from TAVI in this aging population.[3,4]

Frailty describes the loss of strength, endurance, and physiological reserve across multiple body sys-

Heart Metab. (2018) 76:13-17

Abbreviations

CFS: Clinical Frailty Scale; **EFT:** Essential Frailty Toolset; **FRAILTY-AVR:** FRAILTY in older adults undergoing Aortic Valve Replacement study; **OCEAN-TAVI:** Optimized transCathEter vAlvular interventioN-Transcatheter Aortic Valve Implantation registry; **PARTNER:** Placement of AoRtic TraNscathetER valves trial; **STS:** Society of Thoracic Surgeons; **TAVI:** transcatheter aortic valve implantation

tems that increases the risk of dependency or death.[5] Proponents of frailty assessment in TAVI argue that such a holistic evaluation may maximize the benefits by targeting interventions to those most likely to gain functional benefit, while protecting others at excessively high risk from potential harm. However, applying such theories to individualized patient management is not simple. For example, there are over 60 frailty tools in the literature[6] and decompensated heart failure is a well-recognized driver of the frailty state, which may therefore be responsive to TAVI.[7,8] In this review, we summarize the current evidence for the use of frailty assessment to guide the management of older patients with an aortic stenosis.

Studies describing frailty in TAVI patients

The European Society of Cardiology (ESC) guidelines covering patient selection for TAVI have been unable to recommend an optimum tool for frailty, instead suggesting a "heart team" assessment, including cardiologists, cardiac surgeons, and imaging specialists, with the potential to include general practitioners, geriatricians, and intensive care doctors.[9] The lack of consensus around an optimum frailty measure is reflected across the eleven key cohort studies summarized in *Table I*.[10-21] While the mean age of patients

Author, year	Country	Definition of frailty	n	Mean age (years)	Proportion frail (%)	Mortality at 1 year (%)	Relative risk for frail patients (compared with nonfrail patients)
Ewe et al, 2010[13]	Netherlands/ Italy	Fried criteria based on gait speed, grip strength, weight loss, physical activity, and exhaustion	147	80	33	15	MACCE* at 9 months (RR, 4.20; 95% CI, 2.00-8.84) adjusted for logistic EuroSCORE, PVD, previous CABG, and baseline LVEF
Stortecky et al, 2012[14]	Switzerland	Frailty index based on geriatric assessment of cognition, nutrition, timed get-up-and-go, ADLs, and disability. Scored 0-7 with ≥3 considered frail	100	84	49	19	MACCE* at 30 days (RR, 4.78; 95% CI, 0.96-23.77) All-cause mortality at 30 days (RR, 8.33; 95% CI, 0.99-70.48) MACCE* at 1 year (RR, 4.17; 95% CI, 1.37-12.72) adjusted for STS score All-cause mortality at 1 year (RR, 2.93; 95% CI, 0.93-9.24) adjusted for STS score
Rodes-Cabau et al, 2012[15]	Canada	Subjective assessment by a multidisciplinary team	339	81	25	–	All-cause mortality at 42 months (RR, 1.41; 95% CI, 1.02-1.96) adjusted for AF, CVD, COPD, eGFR, and pulmonary hypertension
Kamga et al, 2013[16]	Belgium	SHERPA score (age, ADLs, cognitive decline, falls, and self-perceived health)	30	86	73 (moderate / high risk)	27	All-cause mortality at 1 year (RR, 2.74; 95% CI, 1.39-5.39) per point increase in SHERPA adjusted for sex, BMI, pulmonary hypertension, and diabetes
Zahn et al, 2013[17]	Germany	Presumed subjective assessment (limited detail)	1318	82	18	20	All-cause mortality at 1 year (RR, 1.50; 95% CI, 1.19-1.89)

Table I *Selected studies and outcomes in TAVI cohorts measuring frailty. *MACCE defined as composite of death, nonfatal stroke, heart failure, or nonfatal myocardial infarction. **Poor quality of life defined as Kansas City Cardiomyopathy Questionnaire Overall Summary score <45 or a decrease of ≥10 points on serial testing before and after TAVI. ⁺Only the Bonn subgroup that received frailty assessment was considered from this multicenter study. †Only the development cohort of this study was included. The validation data set does not contain frailty related outcome data.*

Abbreviations: *ADLs, activities of daily living; AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CSHA, Canadian Study on Health and Ageing; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; PVD, peripheral vascular disease; STS, Society of Thoracic Surgeons.*

undergoing TAVI within these studies is consistent (80 to 86 years old), the prevalence of frailty shows significant heterogeneity (5% to 73%), reflecting the nine different tools employed. Subjective or "end-of-the-bed" assessment is the most frequently reported measure, but this is clearly open to variable interpretations by clinicians. In community cohorts, such assessments of frailty demonstrate low sensitivity and specificity for the gold-standard Fried frailty phenotype,[22] which is defined by displaying at least three of five measurable frailty markers: weakness, slowness, low physical activity, weight loss, or exhaustion.[23]

We have previously performed a systematic review and meta-analysis of studies in which frailty measures have been reported in relation to outcomes following TAVI.[24] Across 10 cohort studies and 4592 patients undergoing TAVI, frailty was associated with increased short-term mortality at 30 days (HR, 2.35; 95% CI, 1.78-3.09; *P*<0.001) and later mortality at 1 year (HR, 1.63; 95% CI, 1.34-1.97; *P*<0.001). For this latter outcome, objective frailty tools appeared to identify TAVI patients at the highest risk compared with those classified as nonfrail (HR, 2.63; 95% CI, 1.87-3.70; *P*<0.001). Since this meta-analysis, two major studies including a further 1861 TAVI patients have been reported. The recent FRAILTY-AVR study (FRAILTY in older adults undergoing Aortic Valve Replacement) provided a comprehensive direct comparison of seven different frailty tools in a large multicenter cohort including 646 TAVI and 374 con-

Puls et al, 2014[18]	Germany	Katz index of ADLs (score <6 frail)	300	82	48	28	All-cause mortality at 30 days (RR, 3.05; 95% CI, 1.40-5.70) Minor bleeding at 30 days (RR, 1.50; 95% CI, 1.05-2.16) Renal failure requiring dialysis at 30 days (RR, 2.01; 95% CI, 1.09-3.70) All-cause mortality at 18 months (RR, 2.67; 95% CI, 1.70-4.30) adjusted for age and sex
Seiffert et al, 2014[19]	Germany	CSHA Clinical Frailty Scale[25] (frailty scored at ≥6)	347+	81	5	24	All-cause mortality at 1 year (RR, 1.41; 95% CI, 1.23-1.63) adjusted for age and sex
Capodanno et al, 2014[20]	Italy	Geriatric Status Scale based on ADLs, cognition, continence, and mobility. Scored 0-3 with ≥2 labelled frail	1256†	82	24	–	All-cause mortality at 30 days (RR, 2.09; 95% CI, 1.30-3.37)
Debonnaire et al, 2015[21]	Netherlands/ Italy	Presumed subjective assessment	511	82	19	16	All-cause mortality at 1 year (RR, 1.29; 95% CI, 0.80-2.06)
Green et al, 2015[12]	USA	Frailty score composed of serum albumin, grip strength, gait speed, and ADLs. Scored between 0-12 with ≥6 considered frail	244	86	45	24	All-cause mortality at 30 days (RR, 1.34; 95% CI, 0.59-3.04) All-cause mortality at 1 year (RR, 2.50; 95% CI, 1.40-4.35) adjusted for baseline variables with univariate significance All-cause mortality or poor quality of life** at 1 year (RR, 2.40; 95% CI, 1.14-5.05) adjusted for baseline variables with univariate significance
Afilalo et al, 2017[10]	Canada, USA, France	Essential Frailty Toolset composed of timed chair rises, cognitive impairment, hemoglobin, and albumin levels (frailty scored at ≥3 points)	646	82	37	14	All-cause mortality at 1 year (RR, 3.36; 95% CI, 2.20-5.13) adjusted for STS score
Shimura et al, 2017[11]	Japan	CSHA Clinical Frailty Scale[25] (frailty scored at ≥5 points)	1215	84	29	9	All-cause mortality at 1 year (RR, 1.62; 95% CI, 1.12-2.34) adjusted for logistic EuroSCORE and multiple baseline variables

Table I *Continued.*

Heart Metab. (2018) 76:13-17

ventional surgical valve replacement patients.[10] An even larger cohort of 1215 Japanese TAVI registry patients were assessed using the Clinical Frailty Scale (CFS)[25] in the OCEAN-TAVI study (Optimized trans-CathEter vAlvular interventioN-Transcatheter Aortic Valve Implantation).[11] In both studies, a frail state was independently associated with mortality beyond conventional surgical risk assessments.

The FRAILTY-AVR study compared the frailty phenotype with a further five tools: (i) the CFS; (ii) the Short Physical Performance Battery; (iii) the Bern scale; (iv) the Columbia scale; and (v) the Essential Frailty Toolset (EFT).[10] This latter measure comprises a score between 0 and 5 for completion of 5 timed chair rises (up to 2 points if unable), cognitive impairment measured by a mini-mental state examination (1 point), anemia (1 point), and low serum albumin (1 point). The EFT proved the strongest predictor of 1-year mortality and improved discrimination of the STS score. After adjustment, patients identified as frail by EFT had a 3-fold greater 1-year mortality than nonfrail patients (OR, 3.36; 95% CI, 2.20-5.13).

The CFS provides a brief semiquantitative enhancement to the subjective frailty assessment and was an independent predictor of mortality in the OCEAN-TAVI study beyond the logistic EuroSCORE and standard baseline variables.[11] While it does not require specialist equipment, such as grip strength dynamometers, the CFS necessitates knowledge of symptoms, functional status, and disability. Shimura et al[11] demonstrated that this tool correlated with measurable physical frailty markers, such as gait speed and grip strength.

Outcomes beyond mortality

Despite the variation in frailty tools employed across these studies, there is a clear and consistent link between frailty and poor outcomes after TAVI. The ESC guidelines for TAVI state that patients should have a life expectancy of at least 1 year and be anticipated to gain improvement in quality of life after the procedure.[26] As shown in *Table I*, the majority of patients did survive to 1 year, although 12-month mortality rates varied from 9% to 28% across these studies. For an elderly patient approaching the end of life with symptomatic aortic stenosis, quality rather than quantity of life may take precedence. However, study outcomes to date have focused on mortality after TAVI rather than functional changes in survivors, with the exception of two studies. In the subgroup of patients within the PARTNER trial who underwent frailty assessments, a strong association between frailty and adverse outcomes was observed when a poor or worsening Kansas City Cardiomyopathy Questionnaire score was added to mortality at 1 year as a composite outcome (RR, 2.40; 95% CI, 1.14-5.05).[12] The frailty tool used was an index consisting of physical measures, functional ability, and serum albumin. In the FRAILTY-AVR study cohort, 35% were either dead or more disabled 1 year after TAVI, and preprocedure frailty, measured by EFT, was an independent predictor of this outcome.[10] The Valve Academic Research Consortium also defined important and reportable procedural outcomes after TAVI, including stroke, major bleeding, and the requirement for renal replacement therapy. Unfortunately, data on these outcomes in relation to frailty status is limited.[27]

Choice of frailty tool

The weight of evidence is therefore converging on the use of a specific tool rather than subjective assessments of frailty. The inclusion of physical measurements, such as timed chair rises or gait speed, have demonstrated incremental value in the prediction of functional recovery after TAVI, rather than simply a risk of death. The aim of frailty assessments should not be to deny patients the potential symptomatic benefit achieved through a successful TAVI procedure,[2] but to help make informed discussions using an individualized risk assessment. Frail patients undergoing TAVI could be targeted for additional periprocedural support, including involvement of specialist geriatric services. It is arguable that clinicians seeking the tool with the best evidence to predict the likelihood of a "good outcome" should add the EFT to their routine assessment of patients under consideration for TAVI. The CFS is attractive as a more rapid tool without requiring specific physical or cognitive testing; its inclusion in a consecutive Japanese TAVI patient registry suggests feasibility for adoption into routine clinical care. However, the CFS has not yet been shown to help predict important nonmortality outcomes after TAVI. Crucially, an objective frailty evaluation also identifies a population of patients without frailty, who may otherwise be denied intervention based on a subjective assessment that may bias against the oldest, but fittest individuals.

Conclusions

Frailty assessment in the workup of patients for TAVI provides important information on prognosis that is independent of conventional cardiac surgical risk assessment. The use of objective measurement tools has the potential to improve individualized decision-making in an older population at risk of harm or limited benefit from invasive interventions. ■

Funding sources: *Dr Anand is supported by a Clinical Research Fellowship from Chest, Heart and Stroke Scotland (RES/Fell/A163) and Professor Mills by the Butler Senior Clinical Research Fellowship from the British Heart Foundation (FS/16/14/32023).*
Disclosures: *The author declares no conflicts of interest.*

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Heart Metab. (2018) 76:18-22

Cardiac surgery in the frail patient: managing the increased risks

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Abstract

Frailty, as a reflection of biological age rather than chronological age, has been shown to predispose cardiac surgery patients to higher in-hospital mortality, major morbidity, institutional discharge, and reduced mid-term survival. With an increasing cardiovascular risk burden and the growing adoption of minimally invasive techniques for high-risk elderly patients deemed unsuitable for open surgery, the number of frail patients presenting for cardiac interventions is set to rise over the next few years. Identifying this vulnerable group of patients using comprehensive risk scoring systems, including frailty assessment tools, as well as disability and comorbidity assessments, helps individualize management to the physiological capacity of each patient and optimize the use of limited health care resources. Perioperative nutritional supplementation, physical rehabilitation, and pharmacological agents, together with a balanced anesthetic technique, may benefit the frail patient presenting for cardiac interventions. ■ *Heart Metab*. 2018;76:18-22

Keywords: frailty; pathophysiology; pre-habilitation; sarcopenia

Introduction

Frailty is a concept that describes an impaired capability of an individual to recover from pathological or iatrogenic stressors.[1] Frailty is different from disability, as disability is the impaired ability to carry out functional tasks.[2] While the elderly may be frail, the frail individual may not be elderly. The pathophysiology of frailty is believed to be attributed to immune, endocrine, and metabolic dysfunction.[3] Increased inflammatory cytokines coupled with dysregulation of energy metabolism lead to a catabolic state, giving rise to "sarcopenia." Age-related decline and chronic diseases further potentiate this catabolic state and contribute to multiorgan dysfunction, impairing the homeostatic ability of the frail patient during a period of stress.[3] *Figure 1* describes the pathophysiology of frailty.

In cardiac surgery, frail patients were found to be at an increased risk of in-hospital mortality (odds ratio, 1.8; 95% CI, 1.1-3.0) and institutional discharge (odds ratio, 6.3; 95% CI, 4.2-9.4), as well as having reduced mid-term survival (hazard ratio, 1.5; 95% CI, 1.1 2.2).[4,5] These effects of frailty were independent of age. The use of 5-meter gait speed as a single measure of frailty, independently predicted operative mortality (odds ratio, 1.11 per 0.1 m/sec decrease in gait speed; 95% CI, 1.07-1.16) as well as the composite outcome of mortality or major morbidity.[6]

Abbreviations

CAF: Comprehensive Assessment of Frailty; **EuroSCORE:** European System of Cardiac Operative Risk Evaluation; **PREHAB study:** PRE-operative rehabilitation for reduction of Hospitalization After coronary Bypass and valvular surgery; **PROMM:** Predicted Risk of Mortality or Major Morbidity; **STS:** Society of Thoracic Sugeons; **TAVI:** transcatheter aortic valve implantation

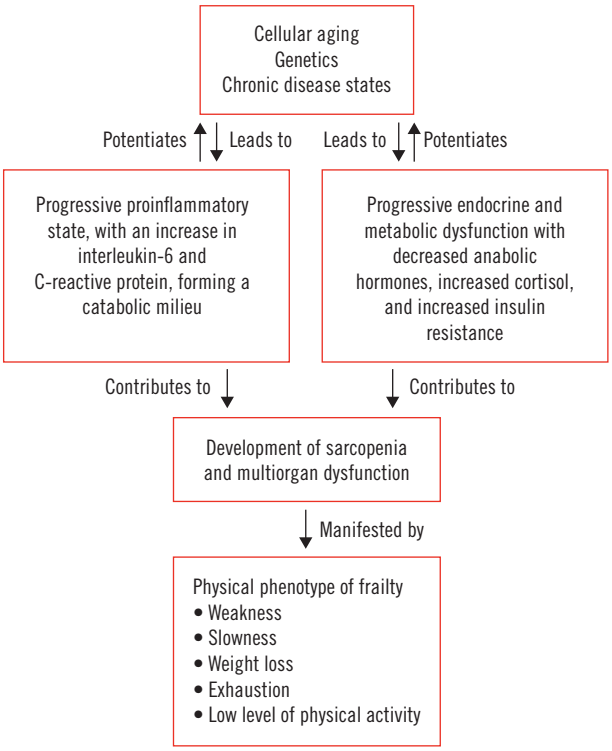

Fig. 1 *Flow diagram describing the pathophysiology of frailty. Cellular aging, chronic disease states, and genetic variation contribute to the development of a progressive proinflammatory state and endocrine and metabolic dysregulation. A catabolic state ensues, which further potentiates their root causes, leading to a vicious cycle and giving rise to multiorgan dysfunction and sarcopenia. The physical phenotype of frailty subsequently manifests in the form of weakness, slowness, weight loss, exhaustion, and low levels of physical activity.*

In transcatheter aortic valve implantation (TAVI) procedures, frailty was an independent predictive factor of increased late cumulative mortality risk (hazard ratio, 1.28; 95% CI, 1.10-1.49) and it was associated with poorer quality of life at 1 year.[7,8] Similar results were reported for aortic surgery, where the unadjusted 30-day/in-hospital and 1-year composite major morbidity and mortality outcomes were significantly worse for frail vs nonfrail patients.[9] In addition to poorer outcomes, the median cost for hospitalization for cardiac surgery was higher in frail patients compared with nonfrail patients, thereby increasing the economic burden on both families and societies.[10]

Risk scoring

Traditional cardiosurgical operative risk scoring, such as the European System of Cardiac Operative Risk Evaluation (EuroSCORE) and Society of Thoracic Surgeons (STS) scores are predominantly based on a comorbidity assessment.[11-15] These scores do not consider frailty, which contribute to the physiological vulnerability of the patient.[11-15] The Comprehensive Assessment of Frailty (CAF) score developed by Sündermann et al has been found to correlate significantly with observed 30-day mortality.[16] At 1 year, a condensed version of this CAF score performed better than the STS and EuroSCORE in estimating mortality risk.[17] Scoring systems that have been described for use in the cardiac surgery population can be categorized into the domains of frailty, disability, and comorbidity.[18]

In the domain of frailty, various methods have been used for assessment, including:

- Physical phenotype, using the Fried Criteria[19];
- Physical performance, using 5-meter gait speed and handgrip strength;
- Sarcopenia, using psoas area and volume;
- Expert judgment-based tools, using the Clinical Frailty Score,[20] which is based on functional performance and independence: ranges from 1 (robust health) to 7 (complete functional dependence on others); and
- Multidimensional tools (including physical, cognitive, performance, self-rated health, psychological, social aspects), using the CAF score[16] (Fried criteria,[19] physical performance test, Clinical Frailty Score,[20] laboratory values of albumin, creatinine, and forced expiratory volume in 1 second, body mass index score), and the Edmonton Frail Scale[21] (9 domains: cognition, continence, functional independence, functional performance, general health status, mood, nutrition, social support, use of medication).

In the domain of disability, assessment tools that have been used include:

- Nagi Scale[22] (including difficulty pulling or pushing large objects, bending, crouching, kneeling, extending arms above the head, handling small objects with fingers, lifting more than 5 kg weight); and

Heart Metab. (2018) 76:18-22

- Activities of Daily Living[23] (bathing, dressing, toileting, transferring, continence, feeding).

In the domain of comorbidity, scoring systems include:

- Parsonnet Score[24];
- EuroSCORE II[13]; and
- STS-PROMM (Predicted Risk Of Mortality or Major Morbidity).[14,15]

While there is significant heterogeneity in the criteria used for frailty and postoperative outcomes in the referenced studies, strong evidence exists for an association between frailty and adverse outcomes in cardiac surgery. Hence, incorporating standardized and validated scoring systems that include clinical, frailty, and disability assessments, as part of the preoperative evaluation process, will help identify patients at high risk of poor postoperative outcomes. With valid outcome estimates, the surgeons can formulate the best treatment options for their patients and help patients make informed decisions regarding their care.

Perioperative intervention

Pre-habilitation, nutritional supplementation, and pharmacological therapies have been described,[25-27] some showing an improvement in outcomes, but evidence in the frail patient is lacking.[28,29] The length of stay in the intensive care unit and hospital were reduced after coronary artery bypass grafting surgery in low-risk patients who had been subjected to a preoperative 10-week exercise regimen; in addition, preoperative inspiratory muscle training has the potential to decrease the risk of respiratory complications.[28,29] Ongoing studies may give us clearer answers to these questions. The PREHAB study (PRE-operative rehabilitation for reduction of Hospitalization After coronary Bypass and valvular surgery), a multicenter randomized controlled trial, compared an additional 8-week exercise and education program at a certified medical fitness facility to standard of care for frail patients to determine if pre-habilitation improves 3- and 12-month clinical outcomes in elective cardiac surgery.[30]

An international multidisciplinary expert group on nutrition in cardiac surgery recommends determining nutritional risk as part of the preoperative assessment and commencing nutritional supplementation in malnourished patients at least 2 to 7 days before cardiac surgery. Postoperative nutrition should also be restarted within 24 hours of surgery and at least 80% of the target requirement achieved by the third postoperative day, with a view of adding immunomodulating components in complex or prolonged surgical procedures.[31] Current pharmacological interventions include protein and vitamin D supplementation for sarcopenia, or anabolic steroids and growth hormones to improve strength, but evidence supporting these interventions is poor.[32]

A multidisciplinary and multidimensional approach to the care of elderly patients involving geriatricians and using the Comprehensive Geriatric Assessment to evaluate functional ability, as well as physical, cognitive, and mental health has been reported.[33] Although this approach may improve postoperative outcomes and reduce postoperative length of stay in elective surgery, evidence in the cardiac surgical setting is lacking.[34,35]

Anesthesia for the frail patient presenting for a cardiac intervention

While there are no published recommendations on anesthesia for elderly frail patients presenting specifically for cardiac surgery, it is reasonable to assume that the same principles for noncardiac surgery will apply. The recommendations from The American Geriatric Society Best Practice Report that are relevant to cardiac surgery include avoiding benzodiazepines as much as possible, selecting glycopyrrolate as the anticholinergic agent of choice, providing adequate pain control, and titrating the depth of anesthesia according to processed electroencephalogram monitoring to minimize the risk of postoperative delirium.[35] Elderly patients are also more prone to postoperative respiratory failure due to inspiratory muscle atrophy and change in lung mechanics. Preoperative counseling should include the risk of potential prolonged postoperative mechanical ventilation, especially after complex cardiac surgery.[36] In addition, altered baroreceptor and adrenoceptor responsiveness lead to increased intraoperative hemodynamic instability and unpredictable sensitivity to vasoconstrictors and inotropes commonly used in cardiac anesthetic practice. Hyperglycemia has been linked with poorer neurocognitive outcomes, among other problems, especially in predisposed elderly individuals, and the latest guidelines by the Society of Thoracic Surgeons

recommend a perioperative glucose target below 10 mmol/L.[37,38] Prudent temperature management on cardiopulmonary bypass may decrease the risk of postoperative cognitive impairment.[39] Additional care must also be taken with intraoperative patient positioning and padding of pressure points, paying special attention to skeletal deformities, such as kyphoscoliosis, especially in cardiac surgeries that are typically longer than other types of surgeries.

Delirium in the frail patient

Delirium is one of the most common complications after cardiac surgery, occurring in up to one-fifth of the patients after cardiac surgery.[40] Postoperative delirium accounts for significant morbidity, increased rates of delayed institutional discharge, cognitive impairment, and mortality.[41,42] There is no effective treatment for delirium, hence it is important to identify at-risk patients early and have resources directed at preventive measures.[43] The Clinical Practice Guidelines that were recommended by the American Geriatric Society for managing postoperative delirium in the general surgical patient, recommend a number of pharmacological and nonpharmacological interventions.[44] The society strongly recommends that a multidisciplinary team administer nonpharmacological interventions to at-risk patients to prevent delirium. These interventions include improving sleep quality by using nonpharmacological sleep protocols and better sleep hygiene, promoting early mobility and physical rehabilitation, providing visual and hearing aids, helping with cognitive reorientation, and ensuring adequate fluid and caloric intake, bowel movement, and medication use.

Conclusions

Going forward, there are two main challenges in managing the frail patient presenting for cardiac interventions. First, a standardized and validated method to assess frailty that is practical and reproducible by both specialists and nonspecialists needs to be created to identify at-risk patients better to facilitate appropriate risk counseling and management. Second, the types and timing of perioperative nutritional, physical, and pharmacological interventions that will improve outcomes for the frail patient need to be determined. The use of a robust risk scoring system, together with a multidisciplinary approach to nonpharmacological and pharmacological interventions, will allow for greater patient-centric care and improve medical and functional outcomes in this high-risk group of patients after cardiac intervention. ■

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Heart Metab. (2018) 76:23-26

Trimetazidine in the frail patient

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Abstract

Frailty encompasses a coexistence of medical factors that reduce resistance to endogenous and exogenous stressors and increase morbidity and mortality. The prevalence of frailty increases with age and in females. Frailty is an important factor to consider in the management of cardiovascular disease (CVD). Patients with CVD often have several overlapping chronic conditions that often require medical therapies, which may negatively affect concurrent diseases. To prioritize treatment strategies, it is necessary to recognize frailty and unnecessary polypharmacy early. Some cardiac medications should be used cautiously in frail patients with CVD as their use may increase the risk of serious adverse events. β-Blockers are associated with an increased risk of cognitive decline and a reduction in the ability to independently perform activities of daily living. Therefore, in frail and highly vulnerable elderly patients, it is best to avoid prescribing β-blockers, especially when they are not strictly needed. Ivabradine is well tolerated in frail elderly patients with comorbidities and is a sound alternative to β-blockers. ACE inhibitors and indapamide can also be used in frail patients and patients with multimorbidities. Trimetazidine is effective and safe in elderly patients with CVDs and multimorbidities; it also significantly reduces the frequency of angina attacks and contributes to the positive dynamics of the indicators of quality of life in elderly frail patients. Therefore, for treating frail patients with CVD, priority should be given to drugs that have a positive effect on functional capacity and quality of life. ■
Heart Metab. 2018;76:23-26

Keywords: cardiovascular disease; frailty

Introduction

Frailty refers to older adults who are at an increased risk of poor clinical outcomes, such as increased mortality, hospitalization or rehospitalization, disability, cognitive decline, and falls. The term comprises a compendium of medical factors that negatively influence the physiological state (physical capability, mobility, cognitive function) and reduces resistance to endogenous, exogenous, acute, and chronic stressors, thereby facilitating increased clinical exposure to adverse outcomes. The term frail, from the Latin fragilis (easily broken), is no longer confined to geriatrics and gerontology, but now extends to all domains of medicine, particularly cardiovascular medicine.

Epidemiological studies indicate that the prevalence of frailty increases with age, resulting in with nearly 7% of people >65 years old and more than 45% of people >85 years old being frail. In addition, the prevalence of frailty is greater in females and in residents of long-term care facilities.[1] As patients with

Heart Metab. (2018) 76:23-26

Abbreviations

ACE: angiotensin-converting enzyme; **CVD:** cardiovascular disease; **NYHA:** New York Heart Association

cardiovascular disease (CVD) age, it is easy to understand why frailty has become an important factor to consider in the management of CVD. Indeed, the increased life expectancy of the general population and the reduced mortality from acute cardiac events have changed the epidemiology of CVD, with an increasing number of patients with chronic heart diseases. Since the prevalence of most chronic diseases increases with age, many older patients now suffer from a higher number of overlapping chronic conditions, which is also known as multimorbidity. Multimorbidity is not the only contributor to frailty, with age-related loss of muscle mass (sarcopenia), reduced nutritional intake, low physical activity and disability (defined as difficulty or dependency in carrying out activities necessary for independent living), and cognitive impairment all playing key roles in determining the frailty phenotype.[2-3]

Although the concept of frailty is well accepted, there is still a lack of standardized instruments for its assessment. In addition, many older adults are not frail, meaning that chronological age, in most cases, neither provides a reliable estimate of biological age nor of how the prevailing underlying disease may affect frailty. Therefore, different frailty models may differently identify frailty as multimorbidity, polypharmacy, and nutritional status. In the frail cardiac patient, the underlying CVD is often the main disease leading to unfavorable outcomes and disability, but, in some instances, other diseases may be more prevalent; therefore, identifying the disease associated with an unfavorable outcome is the key to prioritizing treatments in frail patients.[4-5]

Frailty influences the effect of drugs, as drugs used to treat a given disease may negatively affect other concurrent diseases. Therefore, frail patients are also vulnerable to clinically important drug-to-drug interactions and adverse drug reactions. Frail cardiac patients are often hospitalized due to adverse drug reactions or interactions between cardiac and noncardiac medications. Polypharmacy is associated with a higher incidence of frailty and with increased rates of mortality, incident disability, hospitalization, and emergency department visits in frail and prefrail older adults, but not in nonfrail adults.[6] Since most of these events are often preventable,[7-10] early recognition of frailty and unnecessary polypharmacy is warranted. However, if the cardiac disease is prevalent, the potential negative effects of cardiac medications on other metabolic or neurologic diseases should be taken into account without discontinuing the cardiac medications because they are, in many instances, the only drugs favorably influencing prognosis. It is, therefore, important to include the assessment of frailty in the clinical evaluation of older adults in order to guide their management and coordinate better care.

Cardiovascular medications in frail patients with CVD

Caution must be taken with the use of certain cardiac medications in frail patients as they may lead to negative effects on cognitive or functional decline and may result in an increased risk of serious adverse events *(Table I)*. Indeed, recent studies have shown that, among older patients in nursing homes, β-blocker

Drug	Adverse events
ACE inhibitors / ARBs	Hyperkalemia Hyponatremia Renal Failure
Antiplatelets / anticoagulants	Increased bleeding risk
β-Blockers	Confusion Decrease in functional capacity Decrease in mental function Lethargy Postural hypotension Autonomic dysfunction Depression
Calcium channel blockers	Postural hypotension Flushing Headache Edema Constipation
Digoxin	Confusion Toxicity
Diuretics	Gout Hypokalemia (thiazide and loop)
Nitrates	Postural hypotension Decreased baroreflex function Headache Dizziness Weakness or fainting Nausea and vomiting
Ivabradine / ranolazine / trimetazidine	No significant adverse events in multimorbid elderly. Adjust the dose of ranolazine and trimetazidine in impaired renal function

Table I *Possible negative effects of certain types of medications on cognitive or functional decline in frail patients.*
Abbreviations: *ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.*

therapy was associated with a 33% increased risk of cognitive decline and of having a major decline in the ability to independently perform activities of daily living.[11] Steinman et al studied 15 720 patients aged 65 and older (mean age, 83 years; 71% women) who lived in nursing homes and had a previous myocardial infarction. Nearly one-third (30%) of the patients had intact cognition, 52% had mild-to-moderate cognitive impairment, and 18% had dementia. Of these, 8953 patients (60%) were initiated on a β-blocker and 6767 patients (40%) did not receive a β-blocker. Patients on β-blockers were more likely to experience a major functional decline and they had similar rates of rehospitalization, as did patients not on β-blockers. In the subgroup of patients with moderate-to-severe cognitive impairment, patients who received β-blockers were more likely to experience functional decline (OR, 1.34; 95% CI, 1.11-1.61), with a number needed to harm of 36. Similarly, patients with severe functional dependence were also more likely to experience functional decline after receiving β-blockers (OR, 1.32; 95% CI, 1.10-1.59), with a number needed to harm of 25.

Therefore, although β-blockers improve outcomes in patients with a previous myocardial infarction and reduced ejection fraction, it is best to avoid prescribing β-blockers to frail and highly vulnerable elderly patients due to the negative effects on cognitive function. Another potential problem associated with the use of β-blockers is the deterioration of the autonomic responses, favoring the occurrence of orthostatic hypotension and associated falls, despite not having chronic hypotension or fulfilling orthostatic hypotension criteria during clinical examination.

Therefore, to preserve functional status, independence, and quality of life, therapeutic alternatives to β-blockers should be used. Ivabradine is well tolerated in the elderly with comorbidities and is a sound alternative to β-blockers. The recent UK multicenter LIVE:LIFE prospective cohort study showed that ivabradine improved quality of life, functional status, and New York Heart Association (NYHA) class in typical older patients with heart failure, comorbidities, and polypharmacy.[12] Angiotensin-converting enzyme (ACE) inhibitors and indapamide can also be used in frail patients and in patients with multimorbidities.[13-18]

The PROGRESS study (Perindopril pROtection aGainst REcurrent Stroke Study) showed that perindopril improves cognition in patients with a previous ischemic event. Indapamide is the only diuretic that has been prospectively studied in the elderly. The HYVET study (HYpertension in the Very Elderly Trial), although not primarily aimed at frail patients, reported a significant reduction in mortality, stroke, and occurrence of heart failure in elderly hypertensive patients (again not frail).

Trimetazidine in elderly and frail patients

Among antianginal medications, trimetazidine is effective and safe in elderly patients with CVDs and multimorbidities. Early reports of an increased risk of falls with trimetazidine have not been confirmed. Several studies have reported an improvement in left ventricular function, exercise capacity, and muscle strength in elderly patients with ischemic heart failure, most of whom had multimorbidities and were frail. More recently, our group reported that trimetazidine improves muscle performance and reverses the negative effect of aging in animals and humans.[19-24] Our group has also shown that trimetazidine improved left ventricular function and exercise capacity in elderly patients, especially in frail patients with heart failure. We have also shown that, in these patients, trimetazidine improved quality of life and functional capacity.[23-24] The effect of trimetazidine on quality of life parameters seems to be related to the improvement in left ventricular function and to an increase in skeletal muscle strength. The effects seen in patients receiving trimetazidine are most probably related to an improved efficiency of myocardial cells that often suffer from chronic hypoperfusion due to anatomic and metabolic derangements present in elderly patients.

Trimetazidine is an effective antianginal drug in elderly frail patients. In the elderly frail patients included in the TRIMPOL-I study (TRIMetazidine in POLand), trimetazidine significantly reduced the frequency of angina attacks. In the TRIMER study (TRIMEtazidine in eldeRly people), a 3-month treatment with trimetazidine reduced the frequency of angina attacks, reduced the frequency of ST-segment depression on ECG, and contributed to the positive dynamics of the indicators of quality of life. Trimetazidine is well tolerated and improves angina and myocardial ischemia in elderly and frail patients with coronary artery disease. Since trimetazidine is devoid of any significant effect on heart rate and blood pressure, it is extremely well tolerated in most subsets of patients with multimor-

Heart Metab. (2018) 76:23-26

bidities. Therefore, trimetazidine represents an ideal treatment for elderly and frail cardiovascular patients.

Conclusion

Although the role of frailty in determining the therapeutic decision and patient outcomes is clear, the assessment of frailty is not included in the management of patients with CVD or in most contemporary models of outcome assessment. The reasons for noninclusion are not certain, but could relate to concerns about the complexity of measurements or to the lack of widely accepted and standardized approaches. Cardiovascular drugs may impair quality of life and functional capacity in frail patients with CVD. Therefore, drugs that have a positive effect on functional capacity and quality of life in elderly and frail patients are warranted. Trimetazidine is an effective antianginal drug that has been shown to improve myocardial ischemia, exercise capacity, quality of life, and prognosis in elderly patients, most of whom are either frail or multimorbid and either with or without heart failure. ■

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Heart Metab. (2018) 76:27-31

Managing the frail patient undergoing a percutaneous coronary intervention

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Abstract

Frailty describes an enhanced vulnerability to stressors due to a multisystem impairment, leading to a progressive decline in homeostatic reserve and resiliency. It has been associated with worse clinical outcomes following acute coronary syndrome (ACS) and coronary revascularization. Therefore, frailty status should be taken into careful consideration when treatment strategies are planned. Over the last few decades, the average life expectancy has progressively increased, which has resulted in an increasing number of elderly, frail patients presenting with coronary artery disease and requiring a percutaneous coronary intervention (PCI). Although traditional cardiac risk scores can help risk-stratify patients according to clinical end points, they might not help identify frail patients who may benefit from invasive or noninvasive therapy. Here, we describe a case of an 87-year-old man who was admitted to the emergency department with a non–ST-segment elevation myocardial infarction and evidence of multivessel coronary artery disease, with significant comorbidities, including chronic kidney impairment, peripheral artery disease, and chronic obstructive pulmonary disease. His frailty status was carefully evaluated and the risks and benefits of potential management strategies were taken into account by the heart team. He underwent successful staged PCI to his left main stem and right coronary artery with chronic total occlusion, and reported no symptoms on a subsequent follow-up and a significantly improved quality of life. ■ *Heart Metab*. 2018;76:27-31

Keywords: elderly; frailty; heart team; multivessel coronary artery disease; percutaneous coronary intervention

Introduction

An 87-year-old man presented to the emergency department of his local district general hospital with severe chest pain, on a background of crescendo angina despite optimal medical therapy (OMT) over the preceding 4 months. He denied any history of breathlessness, palpitations, syncope, or other cardiac symptoms. His cardiovascular risk factors included sex, age, dyslipidemia, hypertension, and significant peripheral arterial disease (PAD), with noncritical carotid artery disease, previous abdominal aortic aneurysmectomy, and a residual infrarenal aneurysm, for which he was undergoing regular follow-up visits. Furthermore, he also had a medical history of Hashimoto thyroiditis, iron deficiency

Heart Metab. (2018) 76:27-31

Abbreviations

CABG: coronary artery bypass graft; **CKD:** chronic kidney disease; **COPD:** chronic obstructive pulmonary disease; **DAPT:** dual antiplatelet therapy; **NSTEMI:** non–ST-segment elevation myocardial infarction; **NSVT:** nonsustained ventricular tachycardia; **OMT:** optimal medical therapy; **PAD:** peripheral arterial disease; **PCI:** percutaneous coronary intervention

anemia (for which recent hematological and gastrointestinal investigations had been otherwise unremarkable), chronic obstructive pulmonary disease (COPD), and chronic kidney disease (CKD), with an estimated glomerular filtration rate of 30 mL/min/1.73 m^2.

He lived alone in sheltered accommodation, was able to walk independently with a cane, and was relatively independent in his daily activities, although at a progressively slower pace more recently, and requiring assistance with shopping and home cleaning.

On examination, he appeared frail, but not in cardiorespiratory distress, his vital signs were within the normal range, and cardiovascular examination was unremarkable other than a very mild ejection systolic murmur that was audible in the aortic valve area. He was euvolemic with no evidence of peripheral edema. Electrocardiogram (ECG) showed sinus rhythm with inferior Q waves, but no signs of acute ischemia. Chest radiography demonstrated a normal cardiac silhouette and clear lung fields, with no evidence of pulmonary congestion or consolidation. Routine bloods tests confirmed mild microcytic anemia, normal electrolytes, creatinine level of 2.18 mg/dL (normal range, 0.5 to 1.25 mg/dL), and peak troponin of 862.7 ng/dL (normal range <14 ng/dL).

Therefore, he was treated for non–ST-segment elevation myocardial infarction (NSTEMI), with dual antiplatelet therapy (DAPT), a high-dose statin, and low-molecular-weight heparin, and transferred to the coronary care unit. While on the cardiac monitor, he was noted to have frequent episodes of nonsustained ventricular tachycardia (NSVT), during which he remained asymptomatic and hemodynamically stable. An amiodarone infusion was initiated at this point with no further episodes of NSVT.

A subsequent transthoracic echocardiogram showed a nondilated left ventricle (LV), left ventricular hypertrophy (LVH) with inferior wall hypokinesis and lateral wall akinesis, moderate LV systolic dysfunction with an ejection fraction of 45%, grade I LV diastolic dysfunction, moderate mitral regurgitation with posterior mitral valve leaflet tethering, mild aortic valve (AV) stenosis (AV maximum velocity, 2.59 m/sec; mean gradient, 13 mm Hg), mild AV regurgitation, normal atria dimensions, mild tricuspid valve regurgitation, and normal right ventricular size and function.

He underwent an urgent coronary angiography, which revealed severe three-vessel coronary artery disease (CAD), with critical left main stem stenosis, chronic total occlusion of both the left circumflex artery and the right coronary artery (RCA), and an unobstructed left anterior descending (LAD) artery, which provided retrograde collaterals to the RCA *(Figure 1)*. Due to these findings, combined with the patient's comorbidities and cardiovascular risk factors, he was referred to the local tertiary center for consideration for PCI vs coronary artery bypass graft (CABG) surgery. Following discussions with the Heart Team, his overall perioperative risk was deemed too high, with additive and logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) scores of 16% and 60.1%,

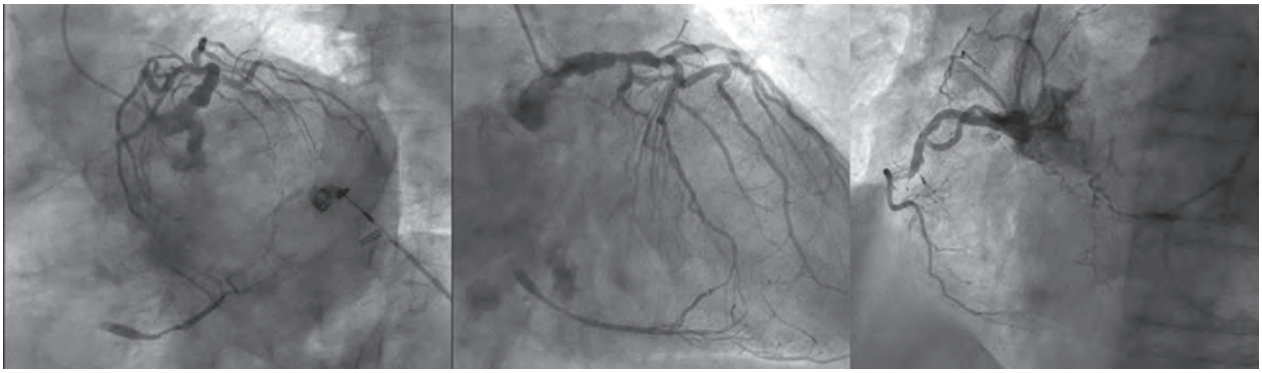

Fig. 1 *Coronary angiography showing critical left main stem stenosis, unobstructed left anterior descending artery with collaterals to the distal right coronary artery, chronic total occlusion of the left circumflex (left and mid panels) and chronic total occlusion of right coronary artery (right panel).*

respectively, a EuroSCORE II of 10.1%, a Society of Thoracic Surgery risk score of 45.1% for morbidity and mortality and 7.7% for mortality.

He underwent urgent PCI to his left main stem using the left radial artery approach, with predilatation using a 3.0 x 12 mm noncompliant balloon, implantation of a 3.5 x 24 mm drug-eluting stent, followed by postdilatation with a 4.5 x 12 mm noncompliant balloon, with excellent final angiographic results *(Figure 2, left panel)*. The patient was then discharged 2 days later on DAPT, with stable renal function and a plan for an outpatient review 4 to 6 weeks later following a dobutamine stress echocardiogram for further assessment of his viable LV inferior wall. This exam showed reversible inferior wall ischemia, for which a staged PCI for the chronic total occlusion of the RCA was advised, following a careful evaluation of the potential risks and benefits and a discussion with the patient. The RCA PCI took place with a dual right femoral and left radial approach. Successful retrograde recanalization of the RCA via the septal collaterals was achieved via a reverse controlled antegrade and retrograde subintimal tracking (CART) technique following a failed attempt with an antegrade approach. After predilatation of the proximal and mid–RCA with a 3.0 x 15 mm noncompliant balloon, 4 overlapping drug-eluting stents were implanted from the RCA ostium to the distal segment, with good angiographic results *(Figure 2, right panel)*. Periprocedural nephropro-

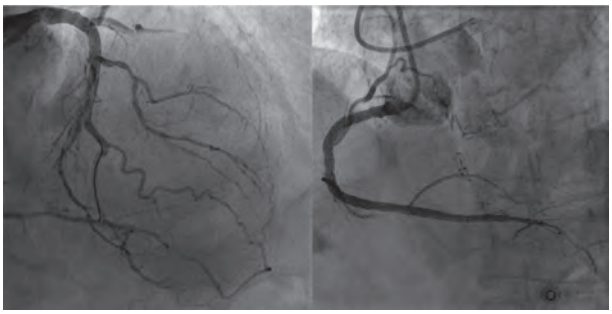

Fig. 2 *Angiographic results following a staged percutaneous coronary intervention to the left main stem (left panel) and right coronary artery (right panel).*

tection was ensured with adequate intravenous hydration, with maintenance of stable renal function. Medical management was suggested for the chronic total occlusion of the left circumflex artery.

The patient was discharged successfully and has remained asymptomatic at subsequent follow-up visits, reporting a significantly improved quality of life.

Discussion

We report a complex case of a frail 87-year-old man, initially presenting acutely with an NSTEMI and evidence of severe multivessel CAD that also involved the LMS, in the context of significant comorbidities, including moderate LVSD, CKD, COPD, and significant PAD, who then underwent a successful staged PCI.

Current guidelines recommend primary or urgent PCI for patients admitted acutely with an ST-segment elevation myocardial infarction (STEMI) or an NSTEMI, respectively.[1,2] Over the last few decades, with an aging population and a progressive increase in cardiovascular risk factors, an increasing number of elderly patients are receiving invasive revascularization.[3] However, these patients are at an increased risk of ACS-related complications, such as bleeding, infections, heart failure, renal failure, and stroke, and the evidence for potential benefits of invasive treatment is limited.[4] A recent meta-analysis[3] that investigated the association between frailty, ACS treatment, and clinical outcomes showed that frailty was independently associated with increased mortality following ACS (adjusted all-cause mortality hazard ratios [HR] for patients with frailty of 1.54-5.39). More importantly, older people with frailty were significantly less likely to receive guideline-indicated ACS care, including PCI, with rates ranging from 6.7% to 43.7% vs 30.4% to 69.5%.[3]

Importantly, recent studies comparing OMT with percutaneous or surgical coronary revascularization for NSTEMI patients >75 years old demonstrated a reduced risk of death and major cardiac events with invasive therapy.[5-7] Crucially, in subjects admitted with STEMI, mortality and morbidity from heart failure, dysrhythmia, and postmyocardial infarction, the complications are significantly reduced with invasive treatment, regardless of the patient's age and despite the increased risk of bleeding in this category.[8] Therefore, this result contradicts the historical clinical practice of a more conservative approach for this patient subset due to the combination of increased risk factors and a relatively short life expectancy.

In addition, a relevant heterogeneity exists within the elderly population, with particular regards to clinical presentation, coronary anatomy, frailty, comorbidities, cognitive impairment, and estimated quality of life, all of which may have a significant impact on procedural and clinical outcomes and should there-

Heart Metab. (2018) 76:27-31

fore be taken into account when evaluating the risks and benefits of OMT vs coronary revascularization in these patients.[3] There is increasing evidence that the potential clinical outcomes in the elderly undergoing invasive coronary treatment following ACS are more related to physiological age than chronological age and that patient frailty constitutes one of the most significant determinants in this regard.[9]

Frailty is a complex syndrome characterized by reduced resilience to stressors and increased physiological vulnerability, with a progressive loss of reserve and physiological function,[10] which has been associated with a significantly higher risk of hospitalization, morbidity, and mortality post–PCI, including a prolonged recovery period, more frequent and severe postoperative complications, such as bleeding, stent restenosis and thrombosis, stroke, and heart failure.[11] This is most likely attributable to the increased inflammatory activation and impaired coagulation cascades observed in this patient subset.[11]

In current practice, the phenotypic frailty models[12] and the frailty index of multiple deficits by Rockwood et al[9] are the most commonly used approaches for assessing patient frailty. The former approaches include the Fried model and the International Association of Nutrition and Aging frailty scale (FRAIL), which are similarly both based on 5 physical indicators; the Fried model is based on grip strength, exhaustion, unintended weight loss, slow gait speed, and low physical activity, while the FRAIL model is based on fatigue, resistance, ambulation, illnesses, and loss of weight.[12] They are favored by physicians caring for the elderly because of their relatively simple bedside use. The Rockwood Clinical Frailty Scale,[11] derived from the Canadian Study of Health and Aging Clinical Frailty Scale (CSHA-CFS), consists of a 9-point scale, from 0 (very fit) to 9 (terminally ill), and it is based on impaired mobility, function, and self-rated health.

A number of studies have been conducted to evaluate the association between frailty, as assessed by the above-mentioned frailty scores, with mortality in patients undergoing PCI, presenting with or without ACS. In a prospective cohort study[13] of 628 patients of at least 65 years of age undergoing PCI, participants were assessed for frailty (Fried criteria), comorbidities, and quality of life: at least 60% of these subjects were deemed frail or intermediately frail, and importantly, the 3-year mortality was 28% for frail patients and 6% for nonfrail patients, with a strong association between frailty and mortality / myocardial infarction (HR, 2.61; 95% CI, 1.52-4.50). Similarly, in another study[14] that included 745 patients undergoing PCI, frail patients required longer hospitalizations after PCI and presented increased rates of 30-day mortality (HR, 4.8; 95% CI, 1.4-16.3; *P*=0.013) and 1-year mortality (HR, 5.9; 95% CI, 2.5-13.8; *P*<0.001), and frailty, as assessed by the CSHA-CFS score, was a predictor of length of hospital stay and mortality, independently of age, sex, and comorbidities.

Interestingly, other studies have often led to conflicting results on the role of frailty in clinical outcomes post–PCI, demonstrating no significant association between frailty and mortality. A recent meta-analysis[3] that included a total of 8 studies and 2332 patients (mean age, 69 years; male sex, 68%; follow-up duration, 30±28 months) concluded that frailty was a significant predictor of all-cause mortality following PCI, with a 2.97-fold increased risk of all-cause mortality (95% CI, 1.56-5.66; *P*=0.001). Importantly, a significant heterogeneity in the pooled HRs was identified, which was mainly due to the different frailty scores used and clinical presentations. Subsequent subgroup analyses demonstrated that both the Fried score and CSHA-CFS were significant predictors of mortality with pooled HRs of 2.78 and 5.99, respectively.

Our patient presented with a FRAIL score of 3, based on fatigue, resistance, and illness, which put him in the frail category of the scoring system. Similarly, based on his CSHA-CFS score of 6, he was deemed moderately frail, as he required help with outside activities and with cleaning his house, as well as minimal assistance with indoor activities. However, the patient was extremely keen to maintain his relative independence and therefore very determined to undergo coronary revascularization. The decision on staged vs "one-time" multivessel PCI was dictated based on the patient's age, frailty, comorbidities, and relevant angiographic findings. In a recent meta-analysis[15] on 1090 patients of at least 60 years of age presenting with NSTEMI and evidence of multivessel CAD, the primary composite end point of myocardial infarction and cardiac death during a 3-year follow-up was not significantly different between the staged and the "one-time" revascularization strategies (7% vs 9.5%; *P*=0.110), and multivariate analysis showed the benefit of staged PCI on the primary events in the elderly (HR, 0.638; 95% CI, 0.408-0.998; *P*=0.049), with a propensity score matched cohort analy-

sis demonstrating that staged PCI was associated with lower rates of primary events (6.1% vs 10.4%; *P*=0.046) and myocardial infarction (3.4% vs 7.4%; *P*=0.037) at 3 years.

Conclusions

The current case report demonstrated successful staged multivessel PCI in a frail patient presenting with NSTEMI, for whom careful consideration was given to multiple factors with a potential impact on clinical outcomes, including age, frailty, comorbidities, and angiographic findings. Older patients referred for PCI should be systematically assessed for frailty status, which should play a crucial role on the final decision of invasive vs noninvasive strategies in this patient subset. ■

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Heart Metab. (2018) 76:32-35

Energy metabolism in the aged heart

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Abstract

Aging is associated with a decline in energy production in the heart that can compromise the ability of the heart to adapt to stresses requiring an increase in energy demand. The main source of energy for the heart arises from mitochondrial oxidative phosphorylation. With aging, mitochondrial function becomes compromised, which can lead to a decrease in energy production and an increase in the production of reactive oxygen species. Impaired energetics in the aging heart can result not only from impaired mitochondrial ATP production, but also from a decrease in metabolic flexibility in the type of fuel used by the heart for energy production, as well as a decreased efficiency of ATP transfer from the site of mitochondrial production to the site of use. Improving both cardiac energy production and the efficiency of energy production may be a novel therapeutic approach to lessen cardiac disease in the elderly. ■

Heart Metab. 2018;76:32-35

Keywords: fatty acid oxidation; glucose oxidation; glycolysis; mitochondria

Introduction

It has been well established that aging is a major contributor to the probability of developing cardiovascular diseases, which includes a marked increase in the incidence and severity of heart failure.[1,2] Aging also results in a number of pathophysiological alterations in the heart, both at a cellular and tissue level, that contribute to an increased risk of developing cardiovascular disease,[1-3] which includes the development of cardiac hypertrophy, arrhythmias, and left ventricular dilatation, as well as alterations in the extracellular matrix, increased cardiomyocyte loss, alterations in calcium homeostasis, apoptotic signaling, autophagy, reactive oxygen species (ROS) generation, and many other key metabolic pathways in the heart.[4] In addition, aging results in dramatic changes in energy homeostasis in the heart, which includes the development of mitochondrial dysfunction.[5] These alterations in energy metabolism are likely to be important contributors to the development of cardiovascular diseases in the aging population. Despite this, our understanding of what effect aging has on cardiac energy metabolism is incomplete and still contradictory. This paper reviews what is known with regard to the effects of aging on cardiac energy metabolism.

Aging effects on mitochondrial function

The heart has a very high energy demand and must produce large amounts of energy, in the form of adenosine triphosphate (ATP), to sustain contractile function.[6] The majority of this ATP production originates from mitochondrial oxidative phosphorylation.[6] In addition to this central role in energy production in the heart, mitochondria also perform a number of other essential functions in the heart, including roles in cal-

Abbreviations

CK/PCr: creatine kinase/phosphocreatine; **CPT:** carnitine palmitoyltransferase; **ETC:** electron transport chain; **GLUT:** glucose transporter; **MCT:** monocarboxylate transporter; **MPC:** mitochondrial pyruvate carrier; **MPTP:** mitochondrial permeability transition pore; **PDH:** pyruvate dehydrogenase; **ROS:** reactive oxygen species; **TCA:** tricarboxylic acid

cium homeostasis, ROS generation, and apoptotic signaling. As a result, situations where mitochondrial dysfunction occurs can have severe consequences on cardiac function, cardiac electrical activity, cardiomyocyte integrity, and cardiomyocyte survival.

Aging results in defects in cardiac mitochondrial function, which are the major reasons for the cellular and organ dysfunction that occurs with aging.[7] These defects include a decrease in cardiomyocyte mitochondrial volume, morphology, and respiration.[8] A key site of these mitochondrial defects is the electron transport chain, which is responsible for mitochondrial oxidative phosphorylation *(Figure 1)*. Mitochondrial defects in the electron transport chain occurs, in part, due to an age-related decrease in transcriptional and functional activity of the mitochondrial oxidative phosphorylation complexes.[7-10] This decrease in mitochondrial respiratory chain enzymes occurs to a larger extent in interfibrillar mitochondria vs subsarcolemmal mitochondria,[7] suggesting that aging compromises ATP supply to the cardiomyocyte contractile proteins. The expression and activity of complex III (cytochrome oxidase), complex IV, and complex V (ATP synthase) are particularly susceptible to aging, while complex I is relatively unaltered.[7,11] A decrease in cardiolipin, the key mitochondrial lipid, contributes to the decreased activity in complexes II-V.[12]

The mitochondrial electron transport chain is also a major site of ROS production in the heart. While the complexes I and III are major sites of ROS production, it is an aging-induced impairment of complex III that appears to be responsible for the increased cardiac ROS production seen with aging.[7,13] Impaired flux through the electron transport chain increases the direct interaction of the reduced redox centers with molecular oxygen to produce the free radical O_2^-, particularly in complex III. The increased ROS production in the aging heart can lead to oxidative damage in the mitochondria, including protein sulfhydryl oxidation, lipid peroxidation, and mitochondrial DNA damage. ROS also acts in mitochondrial metabolism–based stress signaling pathways, including the apoptotic pathway and the mitochondrial permeability transition pore (MPTP) opening. Increased mitochondrial ROS production increases apoptosis observed in the heart during aging.[7] Aging is also associated with an increase in the susceptibility of MPTP opening.[14] An increased ROS production with aging may contribute to this increased opening of the MPTP.[7] The opening of the MPTP can compromise mitochondrial function, increase mitochondrial calcium content, and alter membrane potential, and compromise cardiomyocyte function and survival.

Aging effects on myocardial energy production

Three potential effects of aging on myocardial energy production include: (i) a decreased capacity for energy production; (ii) alterations in fuel selection by the heart; and (iii) a decrease in energy transfer in the heart. These alterations in energy production, energy fuel selection, and energy transfer can negatively affect heart function and contribute to the development of heart failure in the aging heart.

Energy production capacity in the aging heart

The compromised cardiac mitochondrial integrity and the impairments in electron transport chain activity seen with aging are two important contributing factors to a decreased capacity for ATP production in the aging heart, which is associated with a decrease in high energy phosphate levels in the aging human heart.[15] In addition, the tricarboxylic acid cycle (TCA), which is critical for producing reduced equivalents necessary for the electron transport chain, also decreases with aging.[9] This decrease is partly due to a decrease in the expression of a number of genes of the TCA cycle.[10] As will be discussed, acetyl CoA supply to the TCA cycle is also compromised in the aging heart. Combined with the changes in the electron transport chain, mitochondrial oxidative capacity can drop by 50% in the human heart with aging.[16]

Energy substrate selection in the aging heart

Mitochondrial oxidative metabolism can use a variety of carbon substrates to produce the large amount of

Heart Metab. (2018) 76:32-35

energy necessary to sustain contractile function, including the oxidation of fatty acids, pyruvate derived from glucose and lactate, ketones, and amino acids *(Figure 1)*.[6] The majority of cardiac mitochondrial ATP production originates from fatty acid oxidation, although pyruvate from glucose (glucose oxidation) can also be a significant source.[6] Normally, the heart maintains a high degree of metabolic flexibility, switching back and forth between different energy substrates to ensure an adequate energy production by the heart to meet the high energy demand of the heart. However, during aging, this metabolic flexibility is compromised. Unfortunately, there is no good consensus as to what actual switches occur in energy substrate metabolism. While it is generally thought that there is an impaired myocardial fatty acid oxidation and a compensatory increase in glucose metabolism (see reference 7 for a review of this subject), this is not supported by direct measurements of energy substrate flux. Direct measurements of energy substrate metabolism in the heart showed an increase in fatty acid oxidation in aged rats compared with young rats, with a parallel decrease in carbohydrate oxidation.[17] This finding is supported by measurements of gene profiles in hearts of aging humans, in which an increase in fatty acid oxidation genes and a decrease in pyruvate dehydrogenase (the rate-limiting enzyme for glucose and lactate oxidation) was observed.[10] It should be noted, however, that aging-induced increases in pyruvate dehydrogenase have also been observed in the rat heart.[18] As a result, further studies are needed to have a better understanding of what changes in fuel selection occur in the aging heart. It should be noted that inhibition of fatty acid oxidation in the skeletal muscle of aging mice improves glucose and insulin tolerance and protects

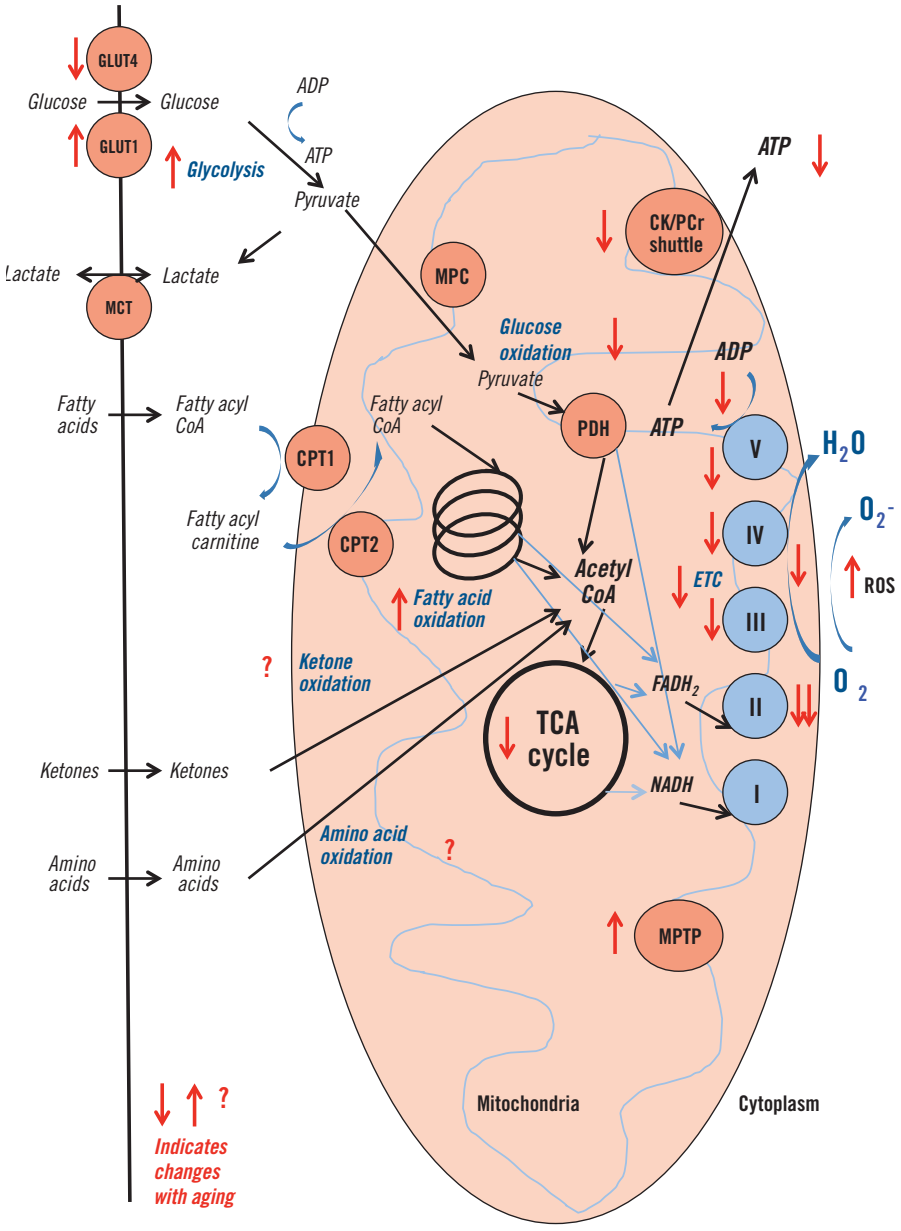

Fig. 1 *Alterations in myocardial energy metabolism in the aged heart. In the aerobic heart, mitochondrial fatty acid oxidation and glucose oxidation are the major sources of energy production in the heart. In the aging heart, both mitochondrial ETC activity and TCA cycle activity are compromised, leading to an impaired production of ATP from oxidative metabolism. Impaired ETC activity can also increase ROS production in the aging heart. The aging heart also becomes "metabolically inflexible" with fatty acid oxidation increasing at the expense of glucose oxidation, a situation that can decrease cardiac efficiency. Glycolysis increases in the aging heart in an attempt to increase ATP production, although this increase in glycolytic ATP production cannot compensate for the loss of mitochondrial ATP production, leaving the heart in a potentially "energy starved" situation.*
Abbreviations: *CK/PCr, creatine kinase/phosphocreatine; CPT, carnitine palmitoyltransferase; ETC, electron transport chain; GLUT, glucose transporter; MCT, monocarboxylate transporter; MPC, mitochondrial pyruvate carrier; MPTP, mitochondrial permeability transition pore; PDH, pyruvate dehydrogenase; ROS, reactive oxygen species; TCA, tricarboxylic acid.*

against age-related metabolic dysfunction.[19] Whether a similar approach may also be beneficial in the aging human heart has yet to be determined.

With a decrease in mitochondrial oxidative capacity and possible decreases in fatty acid and carbohydrate oxidation, the aging heart can become "energy starved," particularly during times of stress or increased energy demand. One attempt to counter this decrease in mitochondrial ATP production is to increase glycolytic ATP production. An increase in the reliance on glycolysis as a source of ATP production has been shown in aging rats and humans.[20,21] However, the amount of ATP produced from glycolysis is small compared with the amount of mitochondrial ATP produced, leaving the potential for the aging heart to remain in an energy compromised state.

Energy transfer in the aging heart

Transfer of mitochondrial produced ATP to its site of use in the cytoplasm requires a creatine kinase (CK)/phosphocreatine (PCr) shuttle pathway *(Figure 1)*. To date, there is no clear consensus as to whether this energy transfer is compromised with aging. Studies have shown no change, an increase, or a decrease in the CK/PCr pathway (see reference 5 for a review of this topic). While decreases in PCr have been observed in aging humans,[22] it is not clear if this is due to alterations in the actual energy transfer process or a decrease in the actual mitochondrial energy production, resulting in a decreased transfer of high energy phosphates from ATP to PCr. While studies have attempted to improve cardiac energetics in the aging heart by altering the CK/PCr shuttle, the results of these studies have not been encouraging.

Conclusions

Aging leads to defects in mitochondrial energy production in the heart, due, in large part, to decreased mitochondrial integrity and decreased activity of the electron transport chain and TCA cycle. Alterations in energy substrate selection contribute to a metabolic inflexibility in the aging heart that may decrease the ability of the heart to deal with pathological stress and increased energy demands, which raises the possibility that therapeutic strategies to improve mitochondrial energy production and metabolic flexibility may be an approach to improve cardiac function in the elderly population. ■

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Heart Metab. (2018) 76:36-39

Exercise and diet for heart disease in the frail patient: fact or fiction?

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Abstract
Frailty represents a state of increased physiological vulnerability and diminished reserve, as well as a complex interaction between age, comorbidities, demographics, and lifestyle. Frailty has repeatedly been demonstrated to be an independent prognostic factor across the spectrum of cardiovascular disease; however, frail patients are often excluded from major clinical trials, leading to a significant gap in the evidence. In this review, we discuss the impact of nutrition and exercise interventions on frailty and, consequently, on cardiovascular disease. ■ *Heart Metab*. 2018;76:36-39

Keywords: frailty; heart disease; lifestyle intervention

Introduction

Over the past decade or so, we have observed a major shift in the nature of the challenges facing cardiovascular clinicians and researchers. Advances in the treatment and prevention of coronary disease have resulted in a diminution in deaths attributable to coronary heart disease. We now live in an aging society, where hypertension remains highly prevalent,[1] heart failure with preserved ejection fraction (HFPEF) is emerging as the most common HF phenotype,[2] and there is a significant increase in nonsurgical percutaneous valve interventions for aortic stenosis. Although age alone cannot be implicated for each of these, it is clear that future developments in the management of cardiovascular disease will be closely intertwined with our understanding of the pathophysiology of cardiovascular aging and its interactions with comorbidities, such as frailty.

The definition of frailty remains challenging; however, at its core, it represents a state of increased vulnerability to external stressors and a decreased physiological reserve. Although the components of frailty are diverse, emerging paradigms include a cycle of immune dysregulation with chronic inflammation, a catabolic state, and progressive sarcopenia, which further contributes to physical inactivity.[3]

Frailty is an independent prognostic factor for both coronary artery disease and heart failure. Within the cardiovascular system,[4] frailty is associated with increased atherosclerosis and coronary calcification, with a reduced vasodilatory capacity, impaired microvascular function, increased arterial stiffness, and increased myocardial fibrosis. Together, these play a major physiological role in the pathogenesis of heart failure. Finally, degenerative diseases of the conducting system and left atrial fibrosis contribute to the

increased prevalence of both bradyarrhythmias and tachyarrhythmias.

Assessing frailty

Frailty has consistently been demonstrated to be a major independent prognostic factor for patients with a variety of cardiovascular diseases, both in the acute and chronic setting and in the periprocedural period. Multiple different scoring systems exist to quantify frailty, with the Fried index[5] being the system most cited in short- and long-term outcome studies, including within cardiovascular disease. The Fried index analyzes five domains (gait speed, weakness, exhaustion, weight loss, and physical inactivity); however, it does not examine cognition or mood. It remains unclear if cognition and mood are part of the pathobiological diagnosis of frailty or if they simply act as a modifier for its impact on quality of life. Of these domains, exercise and dietary counseling, as modifiable factors, can have a significant impact on outcomes.

Treating cardiovascular disease in the elderly

Coronary artery disease

The elderly represent the fastest growing group of patients being referred for cardiac surgery; however, newer interventional and structural techniques have reduced the need for major operative care. Traditionally, predicting outcomes following both percutaneous coronary intervention (PCI) and cardiac surgery have been limited in accuracy in elderly patients, with a tendency to overestimate mortality. In this setting, frailty assessments have demonstrated an independent, incremental benefit in predicting adverse outcomes, particularly concerning gait speed, disability, and quantification of comorbidities.[6] In patients undergoing PCI, frailty was again markedly predictive of mortality, and improved the discrimination of predictive models.[7] Most importantly, the involvement of patients in a dedicated cardiac rehabilitation program improves morbidity and mortality; however, there is a paucity of studies examining frailty that are specifically tailored toward cardiac rehabilitation.

Heart failure

The primary limiting symptom for patients with heart failure is exercise intolerance, measured objectively as peak oxygen consumption at maximal exercise or peak V_{O_2}. Both central and peripheral limitations result in an approximate 35% reduction in peak V_{O_2}, regardless of ejection fraction.[4] It has become increasingly apparent that frailty is a common comorbidity in patients with heart failure, with reduced physical activity leading to sarcopenia, as well as the systemic nature of the disease itself, with direct consequences on the pulmonary and renal systems in particular. Exercise training has demonstrated significant benefit across the spectrum of symptoms and ejection fractions, with a well-established safety profile, although a greater benefit has been seen in patients with heart failure with reduced ejection fraction (HFREF) versus patients with HFPEF. Overall, however, there is a lack of data on guideline-based medical therapy in elderly patients for a multitude of reasons, primarily due to the exclusion of these patients from large-scale clinical trials.

The HF-ACTION trial (Heart Failure and A Controlled Trial Investigating Outcomes of exercise traiNing),[8] an international, multicenter, controlled trial, randomized 2331 patients to 36 supervised exercise sessions followed by home-based training or usual care. The median age was 59 and 20% of the patients were over the age of 70. These patients had a significantly higher comorbidity score, a lower body mass index, and severe systolic dysfunction (median ejection fraction, 26%). Overall, there was a nonsignificant reduction in the primary end point (a combination of mortality or hospitalization), which became significant after multivariate adjustment. Subgroup analysis revealed no significant difference with age concerning the response to exercise training; importantly, age was the strongest predictor of peak V_{O_2},[9] independent of peak heart rate, which is another significant predictor. This noted, age alone only explained 12% of the variance in peak V_{O_2}, meaning that other peripheral factors that contribute to frailty may be explanatory.

The overall impact of exercise-based rehabilitation on heart failure was elegantly summarized in a 2014 Cochrane review[10] that reviewed 33 randomized controlled trials (n=4740 patients). Both patients with HFREF and HFPEF were included, although data on patients with HFPEF were only present in a portion of the four trials. Overall, there was no difference in the 12-month mortality, even though there was a trend toward a reduction at the long-term (10-year) follow-

Heart Metab. (2018) 76:36-39

up. At the 12-month follow-up, admission rates were significantly reduced, quality of life was improved, and support for the cost-effectiveness of exercise-based rehabilitation was demonstrated.

Nutrition, frailty, and CVD

Frailty and nutritional status are closely linked. Unintentional weight loss is a key domain of the original Fried criteria, which may occur due to inadequate energy intake, an important modifiable risk factor. Lowered energy intake is commonly seen with increasing age, and it has been associated with the development of frailty, especially when under the threshold of 25 kcal/kg/day.[11] Protein is a critical factor to maintain muscle mass, with up to 15% of patients over the age of 60 demonstrating intake below the recommended dietary allowance.[12] A careful balance must be struck between adequate intake and avoidance of excessive protein load for a delicate renal system. Although patients able to receive at least 25 to 30 grams of protein have evidence of slowed sarcopenia,[13] large randomized trials have not demonstrated the benefit of higher protein intake in frail patients, which may be due, in part, to impaired synthesis of muscle protein in the context of frail muscle, rather than through lowered protein intake alone.

High sodium intake is also strongly correlated with elevated blood pressure, particularly in older adults.[1] In addition to the vitamins B6 and B12, vitamins C[14] and D[15] have both been independently linked with frailty, although a U-shaped curve is noted with the latter. Vitamin D supplementation improves muscle strength and reduces frailty; however, there is conflicting evidence regarding cardiovascular outcomes, with the most recent data suggesting no significant benefit.[16] Other micronutrients have also been implicated, but this requires further evaluation in large-scale randomized trials.

The Mediterranean diet is considered beneficial for patients with cardiovascular disease. A recent systematic review and meta-analysis demonstrated that greater adherence to the diet reduced the risk of frailty, and the consequent impact on cardiovascular disease will require further investigation.

The gut microbiome has recently become the focus of attention, with significant evidence demonstrating a link with hypertension,[17] heart failure, and other forms of cardiovascular disease. Frail older adults have a less diverse microbiome than younger adults,[18] which may potentially provide a key link between aging, frailty, systemic inflammation, and the development of cardiovascular disease.

Conclusions

Frailty is increasingly prevalent in older patients with cardiovascular disease, remains an independent prognostic indicator of outcomes, and it is modifiable through prescriptive exercise and nutritional counseling. Efforts should be made to quantify frailty using validated scales and target the frail patient, regardless of age, with appropriate lifestyle-modifying therapies to reduce cardiovascular morbidity and mortality. It is well recognized that frail patients are often excluded from major research studies; consequently, there is a drive to encourage trialists to include patients of increasing age, to carefully and objectively measure frailty, and to determine the impact of interventions on slowing the progression of frailty or reversing it. ■

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Heart Metab. (2018) 76:40-41

Activities of Daily Living

Activities of daily living are basic tasks that must be accomplished over a daily timescale for an individual to thrive, including personal hygiene, management of continence, dressing, feeding, and ambulation. Activities of daily living are used as a measurement of an individual's functional status.

Cellular Senescence

Cellular senescence is a cellular stress response characterized essentially by irreversible arrest of cellular proliferation that can occur in response to a potentially oncogenic stress (persistent genomic damage, oncogene activation, epigenomic perturbations), and it involves the activation of tumor suppressor genes. The physiological consequences of cellular senescence include tumor suppression and optimal tissue repair, while the pathophysiological consequences include age-related tumor progression and age-related degenerative alterations.

Clinical Frailty Scale (CFS)

The CFS is a practical and efficient tool for evaluating frailty, which is a condition characterized by increased vulnerability to external stressors. It involves the use of clinical descriptors and pictographs. The scale was designed to aid clinicians in stratifying older adults according to their level of vulnerability.

Comprehensive Assessment of Frailty (CAF) score

The CAF score is another toolset available to clinicians to help assess the risk for elderly patients undergoing cardiac surgery, but unlike other scoring tools (eg, the Society of Thoracic Surgeons [STS] score), the CAF score also includes measures of frailty (eg, weakness, self-reported exhaustion, standing balance, etc) in addition to laboratory data and a patient's clinical features.

Comprehensive Geriatric Assessment (CGA)

The CGA is a multidisciplinary diagnostic and therapeutic intervention pathway that identifies medical, psychosocial, and functional limitations in frail patients. The CGA is intended to help develop a coordinated plan to maximize health with aging.

Endocrine Dysregulation

Endocrine dysregulation refers to disturbances in the regulatory processes (negative feedback and positive feedback control circuits) that govern the release of hormones. As hormones regulate a myriad of physiological functions, endocrine dysregulation can contribute to a broad array of pathophysiological states.

Essential Frailty Toolset (EFT)

The EFT is a simple, but highly predictive composite score of 4 indicators (time to stand five times, cognitive impairment, hemoglobin levels, and serum albumin) used for predicting mortality after transcatheter aortic valve implantation TAVI or surgical aortic valve replacement.

European System of Cardiac Operative Risk Evaluation (EuroSCORE)

EuroSCORE is a European risk score toolset (the American equivalent is the STS score) used to predict operative mortality of adult cardiac surgery within 30 days of the operation or later if the patient remains hospitalized.

Frailty

Frailty is a common clinical syndrome in older adults that increases the risk of poor health outcomes, including falls, incident disability, hospitalization, and mortality. Increased vulnerability results from aging-associated declines in reserve and function across multiple physiological systems. Frailty is operationally defined as the presence of three (of five) phenotypic criteria indicative of compromised energetics: low handgrip strength, low energy, decreased walking speed, low physical activity, and unintentional weight loss (10 lbs/4.54 kg over the course of 1 year).

Left Ventricular Assist Device (LVAD)

An LVAD is a mechanical pump (transcutaneous or implanted in the left ventricle) used to support left ventricular and circulatory function in the setting of heart failure. LVADs are typically used as a bridge-to-transplant therapy or a destination therapy (long-term treatment with an LVAD to prolong and improve patient life).