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Review Article

The importance of the cardiovascular system to the frailty syndrome of the elderly

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Abstract

"Frailty syndrome'' is usually associated with the elderly and is regarded as a generalized state of increased sensitivity that affects mainly the muscular as whell as the cardiovascular system. The correlation between osteoporosis and the poor state of the muscular system, the loss of muscle strength that occurs with aging creates an increased propensity for falls. The correlation between cardiovascular disease and osteoporosis has been vastly attributed to the effects of osteogenic factors such as BMP's (bone morphogenetic proteins), ALP (alkaline phosphatas), OPN (osteopontin) and MPG (matrix Gla protein) on vascular calcifications.Currently, a number of studies are seeking to establish a common pathway also between frailty and cardiovascular disease and the importance of interactions between those two systems. in this short article we are presenting some of these new data.

Keywords: Cardiovascular system, Elderly people, Frailty, Muscular system, Osteoporosis

Introduction

"The eternal mystery
of the world is
its comprehensibility..."
Albert Einstein

The frailty syndrome in the elderly

"The frailty is one of those complex definitions...,
with multiple and 'slippery "interpretations"[1].

The increase in life expectancy observed in the Western civilization in recent decades, has as a consequence the emergence of conditions such as frailty. Frailty is a syndrome that is associated with reduced natural homeostatic reserves as well as a progressive decline in multiple functions of the human body. Usually associated with the elderly, this syndrome is associated with a generalized and progressive condition of sensivity. As a result, it is the reduced resilience that the person presents to exogenous as well as to endogenous stressors. Successfully identified as the focal point between independence and mortality, the frailty syndrome has been "accused" of cases of independent grade disability, increased risk of falling, referral to a hospital, and other co-morbidities. A particularly important point is to differentiate the frailty syndrome with sarcopenia[2].

Conflict concepts around frailty

What is observed is that most, if not all, healthcare professionals and researchers in the wide geriatric field agree to disagree around finding, accepting and using a unique term for frailty syndrome. We find that there is a confusion that leads or may be the result of many different theories and definitions. It would be of particular interest to present a "conflict" or possibly a comparison between the most well-known and universally accepted concepts surrounding frailty such as those of Linda P. Fried and K. Rockwood[3].

Frailty according to Linda P. Fried

The idea behind Linda P. Fried and her team of scientists to find a definition of frailty lies in the fact that the absence of a definition is a major obstacle to successful intervention

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(both diagnostic and therapeutic). The model proposed by Linda P. Fried et al. (2001), is based on the concentration of at least three out of five following characteristics in the "circular" course of progression of the syndrome which is described as follows[3]:

1) Shrinking: Unintentional weight loss greater than or equal to 5 kg in previous year or thereafter (greater than or equal to 5% of body weight in earlier years).
2) Weakness: There is a strong correlation between muscular strength during tightening of the extreme hand and leg function.
3) Reduced resistance and energy: Self-reported tiredness.
4) Sluggishness: Based on the time that the examiner needed to spend one 5 meters (gender and height conversions).
5) Low Body Level Activity: The evaluation was based on the measurement of kilojoules at its level "Baseline".

It is therefore conceivable that in the event of suspicion of susceptibility syndrome, the examiner takes into account the above characteristics. Depending on the number of features presenting in each patient, he is then "placed" in one of the following two categories: 1) Number of Characteristics Classification Greater than or equal to three 3: Categorization Frailty and 2) Number of Characteristics 1,2: Classification "Interim" or "pre-fragile". It is true that the model proposed by Linda P. Fried is found in many studies on frailty, suggesting the universal acceptance of her thinking about this pathological condition[3-6].

According to Dr. K. Rockwood 'frailty'

Dr. Kenneth Rockwood and his scientific collaborators, tried to "move" towards finding a definition of frailty syndrome, with regard to the multifactorial, and simultaneously dynamic nature of this pathological condition. Giving particular importance in integrated gerontological focus points such as the cognitive level, the individual's mobility, the temperance, the functionality as well as him factor of physical exercise, Dr. K. Rockwood and his team supported the theory of "Deficit Accumulation". In this way, it was possible to create and use a frailty assessment index that categorized the patient based on the deficits he presented. The larger the number of deficits that the patient gathered, the greater the frailty that characterized him/her[7-9].

The frailty indicator according to the Rockwood model

The following frailty assessment indicator includes 9 focus points and, together with additional assessment tools, was used in the second phase of the Canadian Study of Health and Aging to evaluate a large number of patients[10-12]. In summary, the proposed model can be described by the following criteria:

- In pretty good physical condition-(01): People who are characterized as active, robust and self-inflicted. There is attachment to a fixed program gymnastics[13].
- Good physical condition-(02): Some patients in this category may complain about memory problems without the existence of objective elements/deficits[13].
- Good management-(03): People whose health problems are controlled in the right way but beyond walking no observe some other physical activity[13].
- Vulnerable-(04): Although independent, the daily activities of individuals of this category are limited by a variety of symptoms. Often signs of fatigue and complaints about reduced walking speed[13].
- Mild form frailty-(05): People in this category are more sluggish on the go and need help to carry out some activities of everyday life[13].
- Moderate form of frailty-(06): If a memory problem causes dependence on other people to perform various daily activities, usually the recent memory will suffer some damage, leaving intact the memories of old events of life[13].
- Serious frailty-(07):Fully dependent on relatives (and not) due to physical but also cognitive dysfunctions. Not a big risk mortality[13].
- Pretty serious frailty-(08): People in this category are totally dependent on others as they approach the end of their lives. Even the recuperation from typical illnesses is difficult[13].
- At the final stage disease (09): Life expectancy is less than six months[13].

Additional commentary-The existence of a variety of indicators aimed at categorizing frailty gives us a sense of confusion in the health sector about the issue of frailty. Also, as can be seen, the method of collecting Rockwood defects can be supported by a large number of health professionals, but it does not cease to be considered a time-consuming process[14,15].

"Observational Studies" that have been carried out in the past, "show" that muscle mass and power take their maximum "value" between the second and fourth decades of a person's life. Muscle strength progressively declines later on and especially the age of sixty. This phenomenon "accompanies" the elderly and during the seventh and eighth decades of his life[16].

The changes found in the muscle tissue with aging are as follows:

- Reduction of motor units.
- Reduce muscle mass and strength.
- Reduce the size and number of muscle fibers.
- Impairment of cross-bridges.
- Falls[9].

A large number of studies have been extensively reported on the mechanism responsible for the observed decrease in muscle mass and loss of fiber as well as muscle function, which is the reduction in the degree of protein synthesis in skeletal muscles. These changes, which characterize the various muscular structures, are best understood through the detailed clinical examination of the physiotherapist. This examination involves firstly palpation and a plethora of special tests that "provide" valuable information about properties such as muscle strength, elasticity, tendency, etc.[14].

Cardiovascular disease is extremely common in the elderly, either due to ischaimia or diseases of the valves. The heart and its function are affected by the changes in vascular system from aging. The inelasticity and hardening of the arteries causes an increase in blood pressure. Some of the most common heart problems in the elderly are: atherosclerosis, heart failure, heart rhythm disorders, coronary heart disease, angina pain, vascular diseases, aortic stenosis, and so on. "Stroke" is a common but non-specific term that describes any impairment of brain function caused by infarction or brain hemorrhage. A more successful term is Cardiovascular disease (CVD), which includes cerebral infarction (thrombosis) or stroke and cerebral hemorrhage due to either parenchymal bleeding (intracerebral hemorrhage) or bleeding in the subarachnoid space (subarachnoid hemorrhage)[17].

Correlation between osteoporosis and cardiovascular disease

Many studies have confirmed the link between cardiovascular disease and osteoporosis. It is known that it is enclosed by cells and that calcification is caused by cells that lead to osteoblasts. It comes from the order of osteoblasts and then hydroxypathy is produced in vitro[18].

Smooth muscle vascular cells have been shown to be transported to such cells that resemble osteoblasts and produce ALP and osteocalcin[18].

Factors for the active role in vascular classification are promoted by the following:

- BMP (bone morphogenetic protein) is a powerful growth factor in osteoblast differentiation and also appears to be an important mediator for vascular calcification. This has been noted in atherosclerotic plaques, where endothelial cells, foam cells, and smooth muscle cells have a higher expression of BMP2 and BMP4. It has been observed in vitro that there are a number of factors that can cause cardiovascular disease such as oxidative stress, low density oxidized lipoprotein (ldl), TNP-alpha may regulate BMR expression in endothelial cells[18].
- ORN (osteoprotein glycoprotein) has the ability to bind hydroxyapatite and calcium, which is expressed in bone tissue and is also found in arteriosclerotic arteries. It is a regulator for the high level of OPN associated with vascular calcification[18].
- Alkaline phosphatase (ALP) has often been shown to increase in vitro in smooth muscle cell cells, especially in the inflammatory state, which is again associated with vascular calcification[18].
- ORP (osteoprotegerin) expressed in vascular and bone tissue is produced by osteoblasts from various factors such as BMP, inflammation, estrogen, vitamin D and oxidative stress[18].
- The RANKL antibody has been shown to inhibit OPG[18].
- With regard to the pathogenesis of vascular calcification and similarities with osteoporosis, the condition of the bones has been shown to be related to factors such as alcohol consumption, hypertension, smoking, physical activity, menopause etc[18].

Radicals have a significant effect on the differentiation of osteoclasts. Oxidative stress is associated with hypertension, atherosclerosis and BMI. Oxidized LDL promotes vascular smooth muscle differentiation in osteoblasts, which is inhibited by antioxidant effects[18].

Mutations in genes related to apolipoprotein E (AROE), osteoprotegerin, and uterine Gla protein are genetically related to bone loss and atherosclerosis. Mice that do not have the osteoprotegerin gene are more likely to develop spinal vascular calcification, osteoporosis, an increased risk of CVD, and cerebral hemorrhage. Similarly, mice that did not have a Gla protein in the uterine gene showed vascular calcifications, osteopenia, and fractures. Vascular disease, end-stage renal disease, risk fractures, hypertension, decreased BMI and, of course,atherosclerosis are related to the ApoE genotype[19].

A cytokine with polymorphism in the IL-6 gene involved in cardiovascular disease and bone metabolism is associated with decreased bone mass in postmenopausal women and increased PAO (increased passive activity observation), while in men the incidence of cardiovascular disease is high. The polymorphism of the vitamin D receptor is associated with a risk of both spinal cord fractures and MI[20].

Other hypotheses suggest a link between them. Decreased blood flow affects intraocular circulation and this leads to osteoporosis. There is evidence that the metal content of hip bones in the affected limb is lower than that of the opposite limb in the case of asymmetric peripheral arterial disease.

Finally, there are indications that certain medications used for osteoporosis and cardiovascular disease, such as antihypertensives, bisphosphonates, statins, and insulin, are effective in both osteoporosis and cardiovascular disease, indicating their common pathology[21].

Raloxifene, a selective estrogen receptor modulator, useful in preventing osteoporosis and risk of fracture, appears to have a positive effect on LDL cholesterol levels and the risk of coronary heart disease, especially in postmenopausal women with improved vascular function[22].

Frailty in older adults with cardiovascular disease: cause, effect or both?

Cardiovascular disease (CVD) has been associated with an increased risk of vulnerability, but the direction of the community remains unclear. In the study of Emma EF. Kleipool et al provides for the examination of the two-way correlation between cardiovascular disease and weakness over an extended period of time. The data of this study come from 1432 seniors, ranging in age from 65 to 88 years of study, who were followed for 17 years. At baseline and follow-up, cardiovascular disease was assessed through the use of medications taken by patients and medical records and thus these incidents were classified:

- to angina,
- myocardial infarction,
- heart failure (HF),
- stroke and
- peripheral arterial disease.

Throughout the study, ingenuity was assessed using Fried's brittleness criteria. Cox regression models showed that patients with heart failure had an increased risk of failure (HR 2.7, 95% CI: 1.5-5.1) after a median follow-up of 8.4 years. This finding was independent of other factors such as age and gender of the respondent. Counter-investigations showed that susceptible older adults had no risk of developing cardiovascular disease. Of all the elderly with cardiovascular disease, those with heart failure have an increased risk of weakness but conversely, susceptible older adults do not have an increased risk of cardiovascular disease. This study demonstrated the community's need for cardiac rehabilitation programs by assessing the impact of physical activity programs to avoid failure and thereby improve the quality of life and independence of care in patients with cardiovascular disease. People with heart failure have an increased risk of weakness and susceptible older adults do not have an increased risk of developing cardiovascular disease[23].

Cardiovascular disease (CVD) as well as vulnerability are widespread among community-dwelling older adults. Life expectancy has increased due to the successes of pharmaceutical and medical research, but this has led to an increase in older people suffering from chronic heart disease[24]. This is a huge financial problem for the health system mainly in western societies. Vulnerability describes a state of weakness due to aging in many physiological systems[25,26] and is associated with a significantly increased risk of falls, disability, hospitalization and mortality[27,28]. According to cross-sectional data, heart disease appears to be positively associated with susceptibility to community-dwelling older adults[29,30]. However, cross-sectional studies do not specify whether heart disease leads to a vulnerability or vice versa. From a pathophysiological point of view, both directions are justified. For example, symptoms (e.g. intermittent bleeding or chest pain caused by exercise) associated with exercise in patients with cardiovascular disease could lead to physical inactivity that would make them more likely to be susceptible to these people. In addition, counts as well as physical and cognitive decline are common in the elderly with cardiovascular disease. This could lead to loss of homeostatic capacity to withstand stressors and increase the risk of vulnerability. However, it could also be argued that physical inactivity and the consequences (e.g. obesity) due to vulnerability are a risk factor for the development of cardiovascular disease Vulnerability is also associated with a chronic state of low inflammation[31] which could cause cardiovascular disease. Therefore, the question of whether cardiovascular disease precedes vulnerability or whether susceptible older adults have an increased risk of developing cardiovascular disease remains to be answered.

Materials and methods used in this study

Study subjects

LASA is an ongoing interdisciplinary study on the physical, mental and social functioning of New York's larger population. Thus, data from this study were used (LASA). Women and women between 55 and 85 years of age, sex, urbanization and expected mortality rate of 5 years were randomly selected from eleven municipal registrars in three different regions of the Netherlands. At the beginning of the period 1992 to 1993, 3107 individuals were registered in these registries and the measurements were made every three years. The data were collected through personal medical discussion in a personal interview of the researchers. Details on sampling and data collection have been described elsewhere[32,33]. Persons born before 1930 (age 65 and over, since January 1996), who participated in the second interview in 1995/96, with information on cardiovascular disease and weakness, were selected for the current study (n=1432). Since the first wave of LASA measurements (1992/3) included various instruments used to assess integrity and because cardiovascular disease was controlled using the subject's medical records in 1995/96, the second wave (1995/6) more data from the first wave and was therefore used as a baseline measurement. Following this second wave (Timepoint 1, T1=1995/96), subjects were followed for a period of 17 years during which follow-up measurements were collected approximately every three years. For the present study, 5 monitoring cycles were used (T2=1998/9, T3=2001/2, T4=2005/6, T52008/9, T6=2011/2). The study was conducted in accordance with the principles of the Helsinki Declaration.

Frailty

Measurements and cutoff limits were identical or similar to Fried's vulnerability criteria[25] during each monitoring measurement (T1-T6). This phenotype includes:
- weight loss,
- Unable to grip force,
- exhaustion,
- slow gait speed and
- low physical activity.

Fried's original cut-off scores were applied to individual phenotype components, except for walking speed and physical activity in which they used the lower quintile approach[34]. This slightly modified vulnerability phenotype has been validated for mortality in the LASA study[35]. Weight loss was present if a person lost 5% or more body weight in the past three years[36]. Body weight was measured without clothes and shoes using a calibrated bath weighing scale of 0.1 kg. Height was measured using a calibrated bathroom

scaling scale, with an accuracy of mm. The body mass index (BMI) was calculated by taking the measured body weight in kilograms and dividing it by the measured height in square meters. The traction force was evaluated with a manual dynamometer (Takei TRK5001, Takei Scientific Instruments, Tokyo, Japan). The sum of the highest values of the two measurements in each hand was used. Initial sex-stratified and BMI cut-off points were applied to indicate weak traction force[25]. Exhaustion was measured using two questions from the Epidemiological Depression Scale (CES-D)[37]. The exhaustion criterion was considered present if a subject responded "frequently" or "most of the time" to the following two statements: "Last week I felt everything I did was an effort" and "Last week I couldn't move". Walking speed was estimated by recording the time it took (in seconds) to walk 3 meters, turn and walk 3 meters back as fast as possible[38]. Slow walking speed was defined by the lowest quintile, stratified by sex and height. Finally, physical activity was assessed using the LASA Physical Activity Questionnaire (LAPAQ)[39]. Low physical activity was determined by the lowest fifth of the average time devoted to physical activity (walking and cycling) per day during the two weeks prior to the interview. Startup data cutoff limits were used in all monitoring metrics[35].

Cardiovascular diseases

The presence of angina (AP), myocardial infarction (MI), heart failure (HF), peripheral arterial disease (PAD) and stroke was assessed at baseline (T1) and during the first follow-up cycle after three years (T2). An algorithm was performed for each specific cardiovascular disease. The presence of these cardiovascular diseases proved satisfactory if there were at least two of the following three criteria:
1) self-reported (symptoms) cardiovascular disease,
2) use of medication specifically during the last 2 weeks or
3) medical records of the physician[40].

If one or more of these specific cardiovascular diseases existed, the cardiovascular disease (combined variable) was rated "yes".

Cardiovascular risk factors, inclusion and polypharmacy

The following cardiovascular risk factors were evaluated:
- age
- sex
- systolic and diastolic blood pressure
- nutritional status (based on BMI)
- use of antihypertensive drugs and statins
- smoking status
- alcohol use
- cholesterol, LDL cholesterol, HDL cholesterol and triglycerides.

Gender and age data were obtained from population censuses.

Blood pressure was measured in a seated position using a standard mercury sphygmomanometer (Omron HEM706 automatic device). Smoking status (never, formerly, current smoker) and alcohol use were assessed using standard questionnaires. Alcohol consumption was classified according to the Garretsen index (no drinking, light and moderate/excessive drinking). Blood samples were taken in the morning, processed, and centrifuged for 60 minutes. The samples were kept frozen at -80°C until determined by the Department of Clinical Chemistry of the VU University Medical Center. Questions on co-morbidity were included in the interview using the Statistics Netherlands chronic illness questionnaire.

Individuals were asked if they had today or previously had one of the following chronic conditions:
- chronic lung disease (asthma and chronic obstructive pulmonary disease),
- arthritis (rheumatoid arthritis or osteoarthritis),
-cancer and
- urinary incontinence.

The presence of diabetes was based on an algorithm that combines self-reporting with the records of a person's physician and the specific diabetes medication. Individuals were asked to collect all the medications they were currently using (prescribed by a doctor and medication without a prescription) and recorded the names and dosages. The anatomical-therapeutic-chemical (ATC) coding and classification system for medication was used to classify these drugs[41]. including the use of antihypertensive and lipid-lowering drugs. Chronic use of five or more drugs has been defined as polypharmacology[42]. The mortality rate and the date of death were obtained from the registries of the municipalities where the respondents lived.

The results of a study of cardiovascular disease on vulnerability among older adults

The present study investigated the two-way effect of cardiovascular disease on vulnerability among older adults living in the community. First, we observed a cross-sectional relationship between cardiovascular disease and vulnerability. Patients with cardiovascular disease, especially those with PAD and HF, were more likely to be vulnerable. In the long run, mainly HF was associated with inability to recruit. These patients were at least twice as likely to become vulnerable, which puts these patients at an equal or greater risk of being vulnerable to people with chronic pulmonary disease, arthritis or diabetes. Analyzing and studying the inverse correlation, we found that in this elderly population, vulnerability does not precede the development of cardiovascular disease over at least three years of follow-up.

Our findings are in line with previous studies on the relationship between cardiovascular disease and vulnerability that show that cardiovascular disease is associated with vulnerability in community-dwelling men and women in cross-sectional data[30,43,44]. However, the timeless elements are not

so sufficient. In the Women's Health Initiative Observation Study (WHI-OS)[45], coronary heart disease, diabetes, and hypertension were specifically associated with susceptibility to incidents after three years of follow-up. Our study adds to these results because we studied a broader spectrum of specific cardiovascular diseases and had more follow-up.

In this study, the results of analyzes with any cardiovascular disease and pneumonia, as well as the incidence of failure, indicate existing compounds, although not statistically significant. However, the magnitude of positive HR, ranging from 1.21 in AP patients to 2.28 in HF patients, makes it possible to correlate between cardiovascular disease and occasional vulnerability. Regarding the cause, the lack of statistically significant correlations and small HRs in the consecutive correlations between vulnerability and incident cardiovascular disease suggests that cardiovascular disease precedes vulnerability, not the opposite. Specifically, the time delay analysis shows that especially patients with HP are at increased risk of vulnerability. However, this should be interpreted with caution given the small number of HP patients.

Existing literature recognizes that patients with HF are more often vulnerable[46,47]. However, much less is known about the effect of HF on vulnerability over time. This 17-year follow-up study shows that HF patients, of all CNS patients, are at greater risk of being vulnerable. How to treat this vulnerable group of patients should require the transition from "problem-based, disease-oriented care" to improving outcomes in "targeted integrated care" in which quality of life and independence (health) care is becoming increasingly important[48].

Some advantages and disadvantages of this study should be recognized. Key Benefits include Long-Term Monitoring for Vulnerability (17 years). In addition, vulnerability assessment is based on installed means and objective measurements, in contrast to many other vulnerability measurements, which are based on questionnaires only. This study is limited to three years between monitoring cycles. Therefore, it is not possible to ascertain at what point in time a matter has become weak. However, this is inherent in most prospective observational studies and an inevitable consequence of research design. This study was also limited to the length of follow-up for a cardiovascular event (three years) and to the relatively low number of patients classified as patients with cardiovascular disease. The latter is probably due to the cardiovascular disease algorithm used in this study, which probably underestimated the actual prevalence of cardiovascular disease in these older adults. Short follow-up for a cardiovascular event may explain the lack of a long-term correlation between weakness and a cardiovascular event.

This study sought to examine the two-way correlation between cardiovascular disease and the risk of integrity over an extended period of time. In conclusion, older adults with HF have an increased risk of vulnerability and susceptible older adults do not have an increased risk of cardiovascular disease. These findings emphasize that treatment regimens in these vulnerable patients should focus primarily on improving the quality of life and independence of care, rather than focusing on the therapeutic aspects of treatment. It also points to the need for prospective cardiac rehabilitation programs to assess the impact of physical activity programs in order to avoid vulnerability. This will improve the quality of life and independence of care, which are important aspects of caring for such vulnerable patients.

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