Obesity and Cachexia in Heart Failure

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Introduction

- Overweight and obesity, which are typically defined by body mass index (BMI) criteria, have numerous adverse effects on general, and particularly, cardiovascular (CV), health
- Obesity is a major risk factor for both coronary heart disease (CHD) and hypertension (HTN), which are the two strongest risk factors for development of heart failure (HF)
- Obesity adversely affects CV structure and function, causing systolic, and especially diastolic, left ventricular (LV) dysfunction

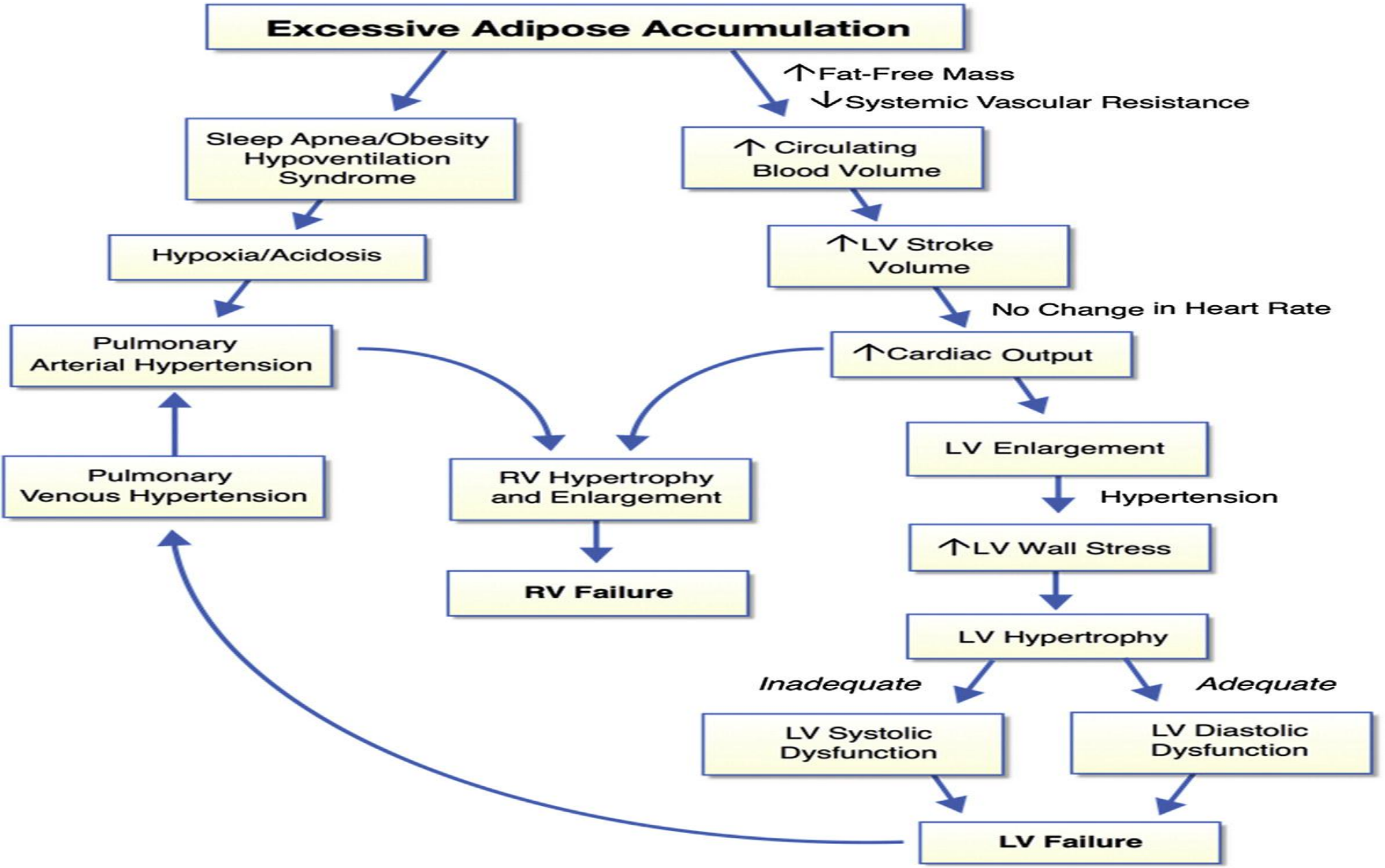
Introduction

- Cachexia is a prevalent pathological condition associated with chronic heart failure
- Its occurrence predicts increased morbidity and mortality independent of important clinical variables such as age, ventricular function, or heart failure functional class
- Clinical consequences of cachexia are dependent on both weight loss and systemic inflammation, which accompany cachexia development

OBESITY AND HF PREVALENCE

- In Framingham Heart Study participants, Kenchaiah and colleagues showed a 5%increase in HF in men and 7% increase in HF in women for every 1 kg/m2 increase in BMI during a 14-year follow-up; the increase in HF risk was noted across all BMI categories.
- In a study of 74 morbidly obese patients, nearly one-third had clinical evidence of HF, with the probability of HF increasing greatly with the duration of morbid obesity; prevalence rates exceeded 70% at 20 years and 90% at 30 years

Pathophysiology



Effects of obesity on cardiac performance

1. Hemodynamics
   i. Increased blood volume
   ii. Increased stroke volume
   iii. Increased arterial pressure
   iv. Increased LV wall stress
   v. Pulmonary artery hypertension
2. Cardiac structure
   i. LV concentric remodeling
   ii. LV hypertrophy (eccentric and concentric)
   iii. Left atrial enlargement
   iv. RV hypertrophy
3. Cardiac function
   i. LV diastolic dysfunction
   ii. LV systolic dysfunction
   iii. RV failure
4. Inflammation
   i. Increased C-reactive protein
   ii. Overexpression of tumor necrosis factor
5. Neurohumoral
   i. Insulin resistance and hyperinsulinemia
   ii. Leptin insensitivity and hyperleptinemia
   iii. Reduced adiponectin
   iv. Sympathetic nervous system activation
   v. Activation of renin-angiotensin-aldosterone system
   vi. Overexpression of peroxisome proliferator-activator receptor
6. Cellular
   i. Hypertrophy
   ii. Apoptosis
   iii. Fibrosis

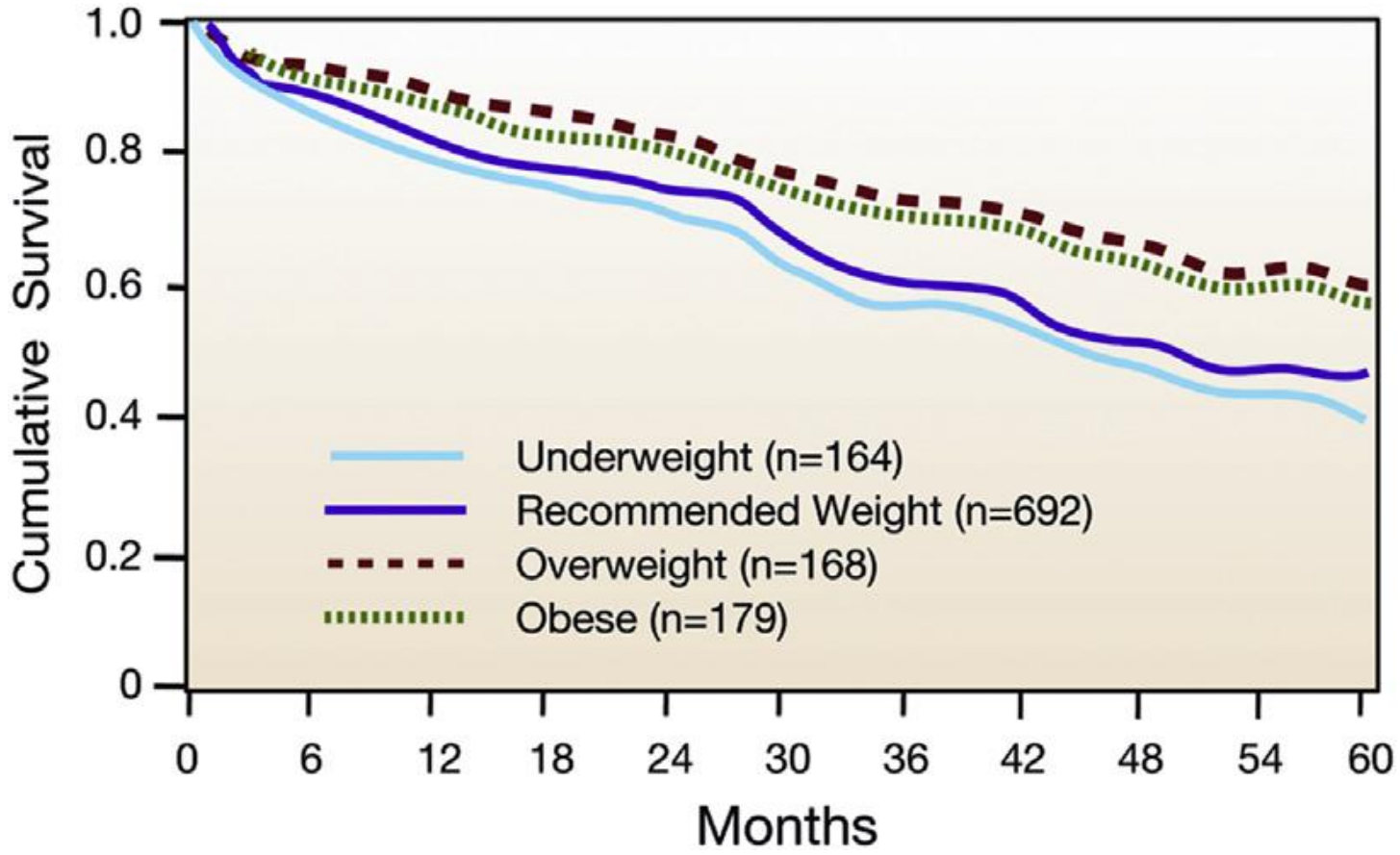
Obesity assessment

Underweight	BMI <18.5 kg/m^2
Normal or acceptable weight	BMI 18.5–24.9 kg/m^2
Overweight	BMI 25–29.9 kg/m^2
Obese	BMI ≥30 kg/m^2
Grade 1	BMI 30–34.9 kg/m^2
Grade 2	BMI 35.0–39.9 kg/m^2
Grade 3	BMI ≥40 kg/m^2 (severe, extreme, or morbid obesity)
Grade 4	BMI ≥50 kg/m^2
Grade 5	BMI ≥60 kg/m^2

OBESITY PARADOX AND HF

- Horwich and colleagues were among the first to show an obesity paradox in HF, in that the best prognosis occurred in the overweight patients with HF
- In contrast, the worst prognosis occurred in the underweight or cachectic patients with HF

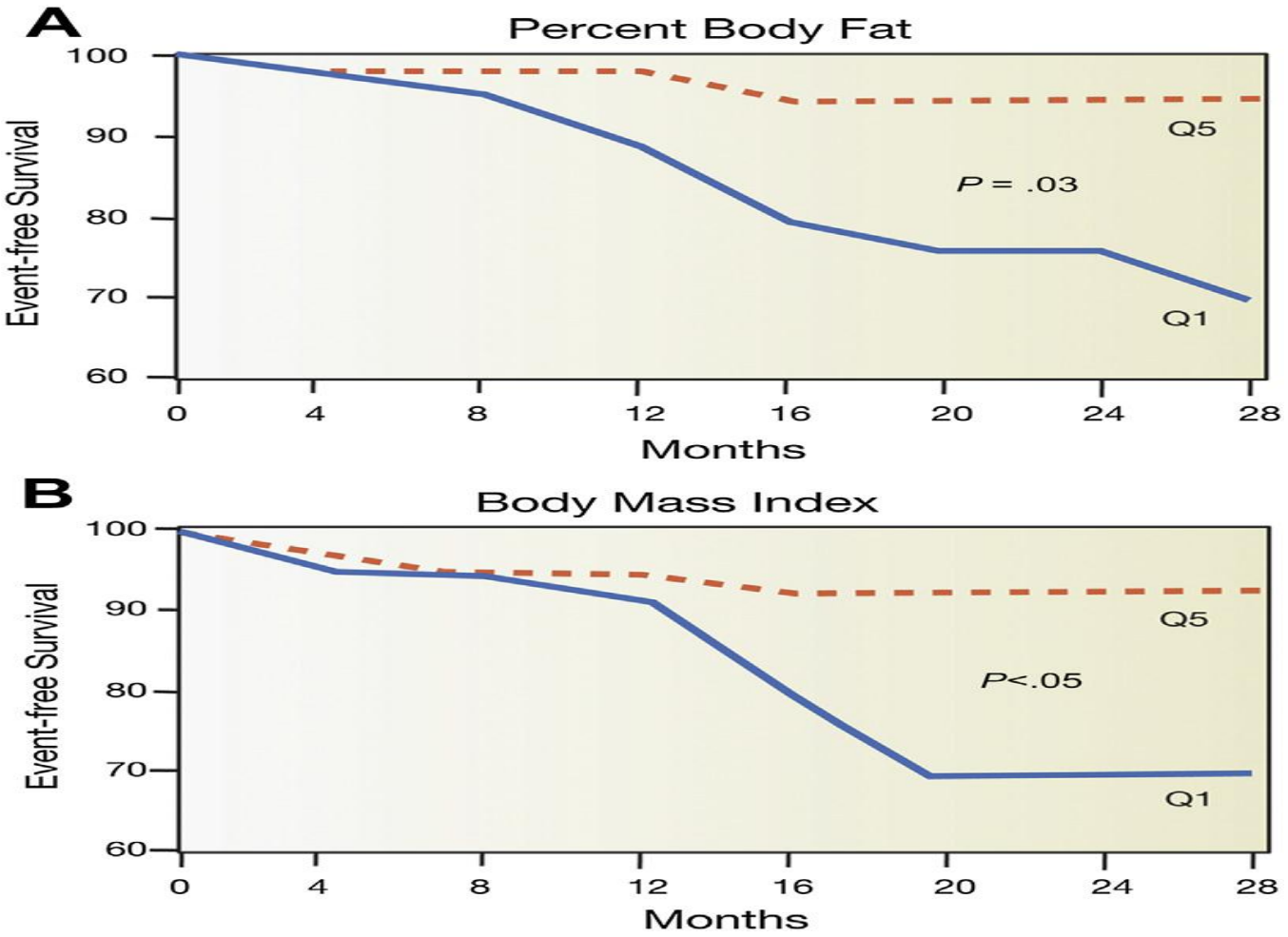
Contd..



Risk-adjusted survival curves for the 4 BMI categories at 5 years in a study of 1203 p atients with moderate to severe HF. Survival was significantly better in the overweight and obese categories

. J Am Coll Cardiol. 2001; 38:789-79

OBESITY PARADOX AND HF



Freedom from cardiovascular death or urgent transplantation in patients in quintiles (Q) 1 and 5 for percent BF (A) and body mass index (B).

OBESITY PARADOX AND HF

- Obesity paradox was noted with percent body fat (BF) as well as with BMI
- Because every 1% increase in percent BF there was a 13% independent reduction in major CV events.
- Study by Clark and colleagues showed that both higher BMI and higher waist circumference (WC) were associated with better HF event–free survival
- Overweight and obese patients with HF had significant reductions in all-cause (16% and 33%, respectively) and CV mortality (19% and 40%, respectively).

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OBESITY PARADOX AND HF

- Adipose tissue is also known to produce soluble tumor necrosis factor alpha receptors, and this could have a protective effect in overweight and obese patients with greater adipose tissue
- Other cytokines and neuroendocrine profiles in overweight/obese patients with HF may be protective.
- Higher levels of circulating lipoproteins in obese patients with HF may bind and then detoxify lipopolysaccharides
- Obese patients in general have an attenuated response to the renin-angiotensin-aldosterone system (RAAS), which may lead to a better HF prognosis

Cardiac cachexia definition

- Cachexia has been defined as at least 5% edema-free body weight loss in the previous 12 months (or a body mass index < 20 kg/m2) in patients with chronic illness and at least three of the following clinical or laboratory criteria:
- Decreased muscle strength, fatigue, anorexia, low fat-free mass index and abnormal biochemistry characterized by increased inflammatory markers [C-reactive protein, interleukin (IL)-6], anemia (Hb < 12 g/dL), or low serum albumin (< 3.2 g/dL).

Cardiac cachexia

- The importance of cachexia in heart failure prognosis became more e vident after the description of the reverse epidemiology of obesity in t his condition.
- Cardiac cachexia prevalence varies between 8 and 42% according to cachexia definition and the study population
- Anker et al.observed that 34% of heart failure outpatients had a ≥ 6% body weight loss during 48 months of follow-up.

Arq Bras Cardiol. 2017 Jan; 108(1): 74–80.

Etiology

- The etiology of heart failure-associated cachexia is multifactorial and the underlying pathophysiological mechanisms are not well established.
- Important factors include food intake reduction, gastrointestinal abnormalities, immunological and neurohormonal activation and an imbalance between anabolic and catabolic processes.

Clinical consequences of cachexia

- Cachexia depend on both weight loss and systemic inflammation, which accompany cachexia development.
- Severe body weight loss, even in the absence of systemic inflammation is associated with deleterious effects on most organs and systems.
- Tissue loss from three compartments, lean tissue, fat mass, and bones is usually found

Clinical consequences of cachexia on heart

- The cardiac consequences of cachexia have been studied in heart disease-free conditions, such as cancer and undernutrition
- In cachectic individuals, left ventricular mass correlated with lean body mass, showing that the heart is subjected to similar consequences to those in lean tissue during cachexia
- Cachexia can also exacerbate heart failure-associated anemia and gastrointestinal changes.

Cachexia prevention and treatment

- Cardiac cachexia is multifactorial, it has been difficult to develop a specific therapy for its prevention and treatment
- Skeletal muscle wasting can precede cachexia, preventive strategies have been largely directed towards muscle mass preservation.
- Currently, nonpharmacological therapy such as nutritional support and physical exercise has been considered as the basis for cachexia prevention and treatment

Cardiac cachexia: perspectives for prevention and treatment

Nonpharmacological approach

Nutritional support

Physical exercise

Drug therapy approach

Treatment clinically useful

Neurohormonal blockade

Reduction in intestinal bacterial translocation by peripheral edema control

Anemia and iron deficiency correction

Experimental use only

Supplementation of essential amino acids

Supplementation of branched-chain amino acids

Appetite stimulants

Immunomodulatory agents (pentoxyphylline, thalidomide, statins, methotrexate, N-acetylcysteine, T-cell activation inhibitors, chemokine antagonists, interleukin-10, interleukin-1 receptor antagonists)

Anabolic hormones (testosterone, growth hormone release-inducing, growth hormone)

Several mechanisms: myostatin inhibitors and antagonists, bortezomide, lipopolysaccharide bioactivity inhibitors, and melanocortin blockers

Nutritional support

- Nutritional support is recommended to obtain and maintain a body weight within or a little below the normal range without edema
- The ingestion of 35 kcal/kg/day was shown to be safe and effective in increasing lean mass in heart failure patients
- Nutritional support should be started with small amounts and slowly increased until desired body weight is reached.

Neurohormonal activation blockade

- Chronic heart failure is characterized by sustained cardiac and systemic activation of the renin-angiotensin-aldosterone and adrenergic nervous systems which, in the long term, impairs ventricular remodeling.
- Blockade of these systems is recommended for all heart failure patients with reduced ejection fraction
- The heart failure control with neurohormonal blockade can reverse cachexia independently of nutritional support.

Reduction in intestinal bacterial translocation

- Heart failure patients with peripheral edema present increased intestine wall thickness, which suggests bowel wall edema
- Cardiac cachexia was associated with intestinal congestion irrespective of heart failure stage and cardiac function
- Heart failure patients also have a reduction in intestinal blood flow and an increase in juxtamucosal bacterial growth
- Intensive diuretic therapy normalized increased endotoxin levels in heart failure patients with peripheral edema

Anemia and iron deficiency treatment

- Anemia is associated with increased mortality, hospitalization, and impaired quality of life.
- Both anemia and iron deficiency are associated with reduced exercise tolerance.
- As decreased exercise capacity is related to a reduced skeletal muscle mass, anemia and iron deficiency may be involved in cachexia development.
- Intravenous iron preparations are safe and effective in treating iron deficiency
- Intravenous iron correction of iron deficiency was associated with improved functional status

Physical Exercise

- Current heart failure guidelines strongly recommend regular physical exercise for stable patients to prevent and/or attenuate cardiac remodeling and skeletal muscle alterations
- Aerobic exercise improves cardiac remodeling and ventricular function, and increases functional capacity and quality of life
- A resistance exercise program improved functional capacity and a combination of hydrotherapy with endurance training improved exercise tolerance and hemodynamic profile of heart failure patients

Future treatment of cachexia

- Appetite stimulants such as megestrol acetate have been used in other cachectic conditions
- In heart failure, repeated Ghrelin administration improved exercise capacity and muscle wasting, suggesting that Ghrelin and its receptor agonist anamorelin may be an attractive approach for future investigation.
- Growth hormone (GH) also have the potential to improve muscle mass and functional capacity
- Currently, several drugs such as myostatin inhibitors and antagonists, bortezomide, lipopolysaccharide bioactivity inhibitors, and melanocortin blockers have been investigated with the purpose of preserving and/or increasing muscle mass in cardiac cachexia.


Thank
You