CARDIAC PACING

REVIEW ARTICLE

Obesity, Weight Loss, Cachexia and Cardiac Resynchronization Therapy: the Good, the Bad, and the Ugly

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ABSTRACT. Obesity has long been known for its deleterious consequences on cardiovascular outcomes. Recent studies have suggested that extra pounds are beneficial for heart failure (HF) patients, while weight loss and cachexia may be markers of poor clinical outcomes in the setting of chronic HF. Nevertheless, the implications of obesity, weight reduction, and cachexia in patients receiving cardiac resynchronization therapy (CRT) is less known. In this short communication, we review current literature on the effects of obesity, weight loss, and cardiac cachexia (the Good, the Bad, and the Ugly) on outcomes in HF patients, with a focus on those receiving CRT. We further offer our perspectives on the clinical applications of current research.

KEYWORDS. cardiac cachexia, cardiac resynchronization therapy, heart failure, obesity.

The Good

Obesity is associated with diabetes, hypertension, coronary artery disease, atrial fibrillation, and obstructive sleep apnea. It has also been shown to result in greater risk of developing new heart failure (HF), with abdominal obesity a potentially more significant risk factor than weight alone. Larger studies have confirmed that patients with moderate obesity experienced the lowest mortality relative to others. Larger studies have confirmed that overweight status and obesity may be associated with better outcomes. In a study of over 1,000 patients with New York Heart Association (NYHA) functional class III–IV HF, elevated body mass index (BMI) did not increase mortality risk and potentially improved survival. Another study showed that patients with moderate obesity experienced the lowest mortality relative to others. Larger studies have confirmed that overweight status and obesity are associated with lower mortality risk. A meta-analysis of nine observational studies and more than 28,000 HF patients revealed a lower risk of all-cause and cardiovascular mortality among overweight and obese patients.

Given this obesity paradox in HF patients, researchers have attempted to shed light on the effects of elevated BMI on benefit derived from cardiac resynchronization therapy (CRT) (Table 1). Clemens et al. reported that obesity and overweight status relative to normal BMI were associated with a higher prevalence of CRT response (obese: 63%, overweight: 71.4%, normal: 44.7%) among HF patients with NYHA III–IV symptoms. Another study of NYHA class III–IV HF patients receiving CRT found that those in higher BMI categories experienced greater reverse remodeling and long-term likelihood of survival free from death, heart transplant, or ventricular assist device implantation. Similarly, in the setting of NYHA class III–IV HF, obese and overweight patients, when compared to normal-weight and underweight patients, benefited from greater improvements in left ventricular (LV) end-diastolic diameter and LV ejection fraction after implantation of CRT. In this cohort, obesity and overweight status were further related to greater CRT response rates (obese: 82.9%, overweight: 77.1%, normal: 52.2%, underweight: 33.3%), as well as a lower risk of mortality and combined end point of death and HF hospitalizations. A higher BMI
The effects of obesity on CRT response

Among CRT patients, obesity has been found to lead to improved long-term likelihood of survival without heart transplantation or ventricular assist device implantation. In a sub-study from the COMPANION trial, reduction in pump failure death was observed in obese relative to non-obese NYHA class III–IV HF patients receiving CRT with pacemaker, but no differences in all-cause mortality and sudden death were observed. A sub-study from MADIT-CRT, which enrolled HF patients with NYHA class I–II symptoms, reported no differences in HF events or death between obese and non-obese CRT patients. While few studies in the literature have examined the impact of BMI on outcomes after CRT implantation, the preponderance of evidence suggests that obesity is linked to greater CRT benefit. Thus, the obesity paradox in HF appears to persist even after CRT implantation. This relationship between obesity and CRT outcomes may further be related to the severity of the underlying cardiomyopathy, whereby excess weight in advanced HF but not mild HF patients appears to improve outcomes. Why do advanced HF patients implanted with CRT do better when obese? It is conceivable that excess body fat signifies metabolic reserves in HF patients, making them less vulnerable to the catabolic state and allowing greater benefit from CRT than in leaner patients. In one study, obese and overweight patients presented with lower baseline risk for non-response to CRT, experienced shorter duration between HF symptom onset and CRT implantation, and exhibited better tolerance of aggressive HF medical therapy, all observations that were described as potential reasons for greater CRT benefit. Further research is thus needed to clarify mechanisms involved in mediating the effects of obesity on CRT response.

The Bad

Based on these findings, it is likely that obesity is protective to the extent that unintentional weight loss becomes harmful. Weight reduction of 7.5% or more during a 6-month period was found to be a predictor of mortality in HF patients. A study from the SOLVD trial reported that weight loss of 6% or more among HF patients was associated with worse survival. In a large cohort of nearly 7,000 HF patients from the CHARMM program, patients with weight loss of 5% or more after 6 months experienced increased risk of death. In these studies, weight loss was found to portend adverse outcomes, despite adjustment for age, NYHA class, and LV ejection fraction. Thus, unintended weight loss in HF patients may be a harbinger of adverse outcomes. Weight loss, even among mild HF patients receiving CRT, has been associated with increased risk of death and HF events.

The Ugly

Unintentional weight loss of greater than 6–7.5% has been proposed to signify cardiac cachexia in HF patients. Cardiac cachexia is characterized by a significant catabolic state, whereby factors including neurohumoral activation, increased inflammatory cytokines, and hormonal imbalances are believed to result in generalized tissue wasting that is a marker of disease progression and poor prognosis. Anorexia and nutrient malabsorption may additionally contribute to cachexia. Findings of decreased muscle strength, anemia, and low serum albumin are also described in cachectic patients.

Table 1: Summary of studies examining the effects of elevated BMI on the benefit derived from CRT.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of patients</th>
<th>Baseline weight categorizations</th>
<th>End point</th>
<th>Main finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clemens et al.</td>
<td>2010</td>
<td>169</td>
<td>Obese versus overweight versus normal</td>
<td>CRT response</td>
<td>Greater prevalence of CRT response in obese (63%) and overweight (71.4%) versus normal (44.7%)</td>
</tr>
<tr>
<td>Rame et al.</td>
<td>2010</td>
<td>1,516</td>
<td>Obese versus normal</td>
<td>All-cause mortality, sudden death, and pump failure death</td>
<td>Reduction in pump failure death in obese but not in normal</td>
</tr>
<tr>
<td>Onishi et al.</td>
<td>2012</td>
<td>316</td>
<td>Obese versus overweight versus normal</td>
<td>Reverse remodeling, long-term survival free from death, heart transplant, or ventricular assist device implantation</td>
<td>Greater reverse remodeling and long-term survival free from death, heart transplant, or ventricular assist device implantation in greater BMI categories</td>
</tr>
<tr>
<td>Cai et al.</td>
<td>2014</td>
<td>247</td>
<td>Obese versus overweight versus normal versus underweight</td>
<td>Reverse remodeling, CRT response, all-cause mortality</td>
<td>Greater reverse remodeling and lower mortality in obese and overweight; greater prevalence of CRT response in obese (82.9%) and overweight (71.1%) versus normal (52.2%) and underweight (33.3%)</td>
</tr>
<tr>
<td>Aktas et al.</td>
<td>2014</td>
<td>994</td>
<td>Obese versus normal</td>
<td>Heart failure events or mortality</td>
<td>No difference in heart failure events or mortality between obese and normal</td>
</tr>
<tr>
<td>Wand et al.</td>
<td>2015</td>
<td>113</td>
<td>Morbidly obese versus obese and overweight versus normal</td>
<td>Long-term survival free from heart transplant or ventricular assist device implantation</td>
<td>Greater long-term survival free from heart transplant or ventricular assist device implantation when BMI category is higher</td>
</tr>
</tbody>
</table>
Research examining the effect of weight loss and cachexia on CRT outcomes is significantly lacking. Further studies involving patients with a range of HF severity are needed to examine the impact of weight loss and cachexia on outcomes after CRT implantation, during short- and long-term follow-up.

Synthesis

What does this mean for the clinician? Despite the association of obesity with better outcomes in HF patients, including those receiving CRT, we believe that intentional gain of surplus body fat should not be recommended. Rather than highlighting the importance of being simply fat or lean, these findings suggest that unintended weight fluctuation is more essential to monitor and detect. There is a particular need to be watchful for unplanned weight loss, so that physicians can thoroughly evaluate such patients and consider intensification of medical therapy when appropriate. In all HF patients, maintenance of stable weight and BMI <30 kg/m² through proper nutrition, regular exercise, and preventive measures in conjunction with optimal medical and/or device therapy is the recommended approach. For the subset of patients with cardiac cachexia, nutritional therapy that is guided by a dietitian and which emphasizes protein intake and fluid and sodium restriction may improve outcomes. Rehabilitation efforts to improve exercise capacity are also beneficial. Pharmacologic agents, including anti-cytokine and human growth hormone-based therapies, do not have proven efficacy or remain investigational.

References