EFFECT OF BETA-ADRENERGIC BLOCKADE ON WEIGHT CHANGES IN PATIENTS WITH CHRONIC HEART FAILURE

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Abstract:

Background:

Weight loss is common in patients with chronic heart failure (CHF) and is associated with adverse outcome. Activation of the sympathetic nervous system has been implicated in weight loss, wasting and cachexia. However, the effect of sympathetic antagonism on weight change in patients with CHF is not well defined.

Methods:

We evaluated changes in body weight, the incidence of cachexia (weight loss > 6%) and significant weight gain (>5%) in unselected patients with CHF due to left ventricular systolic dysfunction (LVSD) (LV ejection fraction (LVEF)<40%) and studied the effect of beta-blockade on weight change.

Results:

Of the 1480 patients enrolled (median NTproBNP:1651ng/L, median LVEF:31%), 86% received beta-blocker, 11% never had beta-blocker and 3% discontinued beta-blocker between baseline and 1 year.

Patients who did not have or tolerate beta-blocker were more likely to develop cachexia (23% vs 10%, p<0.001) and less likely to have significant weight gain (22% vs 24%, p<0.001) than patient who had beta-blocker.

During a median follow up of 1876 days (IQR: 993-3052 days), 894 (60%) patients died. Higher body mass index (BMI) at baseline, weight gain and beta-blocker therapy were associated with better outcome. Patients who had all 3 features: beta-blocker therapy, baseline BMI ≥25 and significant weight gain had the best outcome (22% mortality at 5 years).

Conclusion:

Patients with CHF due to LVSD who receive beta-blocker were less likely to develop cachexia and more likely to have significant weight gain and better outcome compared to patients who did not receive or tolerate beta-blocker.

(249 words)

Key words: heart failure, cachexia, weight change, beta-blocker, sympathetic activation

Introduction:

Many chronic conditions are associated with unintentional weight loss, which can be sufficient to be defined as cachexia when weight loss exceeds an arbitrary limit, often taken to be more than 5% in 12 months.[1] Weight loss can occur from all body compartments; for patients with chronic heart failure (CHF), loss of muscle bulk is particularly important because it leads to reduced exercise capacity and worsened symptoms.[2] The prevalence of cachexia in patients with CHF ranges between 5-15%[3] and is strongly related to an adverse prognosis.[4] Treatment trials in patients with cardiac cachexia have been discouraging so far.

Activation of the sympathetic nervous system secondary to cardiac dysfunction is implicated in the development of muscle wasting and cachexia.[5] Beta-adrenergic blockade reduces muscle catabolism and leads to weight gain in both in patients with cardiac and those with non-cardiac disorders.[6] In the Carvedilol Prospective Randomised Cumulative Survival (COPERNICUS) trial, patients randomised to carvedilol were 33% less likely to become cachectic and 37% more likely to have a significant gain in weight.[7] However, the patients in clinical trials are highly selected patients who may not be representative of the majority of patients with a condition. We wanted to explore the effects of beta-blockade on weight change in unselected patients with CHF to see if these findings are generally applicable.

We explored the effects of sympathetic blockade on weight change and mortality in a large cohort of well-characterised patients with CHF.

Methods

Consecutive patients referred between 2000 and February 2016 with suspected HF by either primary or secondary physicians to a community HF clinic, which serves a local population of about 500,000 people, were enrolled. Some patients had no prior diagnosis of HF and were treatment naive, therefore requiring initiation of guideline-recommended therapy; many others had a pre-existing diagnosis of HF and had already been initiated on treatment that might, however, require optimisation.

Because a beta-blocker is recommended only for patients with HF and reduced left ventricular ejection fraction (LVEF), we included only those patients who had signs or symptoms of CHF and LVEF <40% (or at least moderate left ventricular systolic dysfunction by visual inspection if LVEF was not measured).[3] (Appendix 1)

Only patients who had weight recorded at baseline and at 1 year visit were included. Patients with weight loss of >6% between baseline and 1 year were defined as having cachexia. A higher cut-off than the usual 5% was used to ensure we only included patients with significant weight change, as weight may fluctuate in patients with CHF as a result of changes in fluid status. Indeed, there is also evidence to suggest that a cut-off of 6% weight loss should be used to define the presence cachexia in patients with CHF.[7] Patients with weight gain of ≥5% from baseline were classified as having significant weight gain.[7] For patients who had 3 or more weight measurements recorded between baseline and 1 year visit (N=1361 (92%)), we also determined the variability of body weight by calculating the standard deviation of weight measurements recorded between baseline and 1 year.[8]

All patients had a full medical history and physical examination. Ischaemic heart disease (IHD) was defined as any previous medical history of acute coronary syndrome (ACS), percutaneous coronary intervention or coronary artery bypass surgery, or a diagnosis of myocardial ischemia based on invasive or non-invasive diagnostic tests. Cerebrovascular disease (CVD) was defined as any previous history of stroke or transient ischaemic attack (TIA). Peripheral vascular disease (PVD) was defined as a clinical history of the diagnosis.

Blood was taken for standard haematology, biochemistry profile and N-terminal pro B-type natriuretic peptide (NTproBNP). Patients were weighed in their casual wear without shoes. Body mass index (BMI) was calculated using the formula: BMI = weight in kilograms / (height in meters) squared.

All patients were regularly seen in the HF clinic, usually at baseline, after 4 and 12 months, and then yearly, unless an expedited appointment was requested. HF medications were optimised and diuretic dose adjusted to maintain euvolaemia and dry weight. Weight loss with dietary restriction was not routinely advised for overweight or obese patients, although a healthy diet and regular physical exercise was always recommended.

We classified patients into 4 groups: 1) on beta-blocker therapy at baseline and 1 year; 2) not on beta-blocker therapy at baseline but on beta-blocker therapy at 1 year; 3) on beta-blocker therapy at baseline but not on beta-blocker therapy at 1 year; and 4) not on beta-blocker therapy at either time point. As group 3 had very few patients (N=41 (3%)), we excluded this group from further analysis, although patients in group 3 seem to be sicker than patients in other beta-blocker treatment groups.

We also stratified patients into 3 BMI (kg/m^2) categories: 1) underweight/normal (BMI<25.0), 2) overweight (BMI = 25.0-29.9) and 3) obese (BMI $\geq$ 30.0).[9]

End points and follow-up

Patients were followed up until 9th March 2017. The primary endpoint was all-cause mortality. Our hospital is the only one in the region offering acute medical services. With previous consent from patients, we could access all their primary and secondary care records. Data regarding deaths were collected from the hospital's electronic systems and were entered into a dedicated database, stored on a secure NHS server.

Statistical analysis

Continuous data are expressed as medians with interquartile ranges (IQR) (25th to 75th centiles) and categorical data are expressed as N (%). Independent t tests and non-parametric tests were used to compare medians across ordered groups for normally and non-normally distributed variables, respectively. The chi-squared test was used to compare proportions between groups. Pearson's correlation or Spearman's correlation coefficients were used to assess the relationships between two variables. Log-transformation was applied when the data were very skewed.

Cumulative incidence curves for all-cause mortality were constructed by the Kaplan-Meier method. The relationships between baseline BMI, beta-blocker treatment, degree of weight change and the risk of all-cause mortality were examined using Cox proportional hazards regression models.

All statistical analyses were performed using SPSS 22 (SPSS INc.,Chicago, IL, USA) and The Stata (14th Version, StataCorp, TX, USA) statistical computer package. A two-tailed P value of <0.05 was considered significant in all analyses.

The study conformed to the principles outlined in the Declaration of Helsinki and was approved by relevant ethical bodies. All subjects gave their written informed consent for their data to be used for research.

Results

Patient characteristics

The baseline characteristics of the 1480 patients meeting the inclusion criteria are shown in table 1.

Beta-blocker therapy

Of the 3 beta-blocker therapy groups we focused on, patients who did not have beta-blocker therapy at any point were the oldest, most likely to be female, had the most severe symptoms and greatest signs of congestion. They were also the least likely to be on angiotensin converting enzyme inhibitor or angiotensin receptor blockers (ACEi/ARB). Patients who did not have beta-blocker therapy at baseline but had beta-blocker therapy at 1 year had the highest baseline NTproBNP. (Table 1a)

Cachexia and significant weight gain

Cachexia occurred in 13% (N=185) and significant weight gain occurred in 24% (N=363) of patients. (Table 1b)

Compared to those with significant weight gain or stable weight, those who developed cachexia were older, had higher BMI, worse symptoms and congestion, higher baseline NTproBNP, lower haemoglobin, worse renal function, were less likely to be on ACEi or mineralocorticoid receptor antagonist (MRA) and had a smaller fall in NTproBNP at 1 year. (Table 1b)

Weight change and beta-blocker therapy

The incidence of cachexia was higher in patients who did not have beta-blocker therapy than in patients who had beta-blocker therapy at baseline and 1 year (P<0.001). (Appendix 2a) The incidence of significant weight gain was higher in patients who had beta-blocker therapy either at baseline or initiated between baseline and 1 year than in patients who did not have beta-blocker therapy (P<0.001). (Appendix 2a)

Weight change and baseline BMI

The incidence of cachexia was higher in patients who were obese (BMI $\geq$ 30 kg/m^2) than in patients who were overweight (BMI = 25.0-29.9 kg/m^2) or normal/underweight (BMI <25 kg/m^2) (P <0.001). (Appendix 2b) The incidence of significant weight gain was lower in obese patients than in patients who were overweight or normal/ underweight (P <0.001). (Appendix 2b)

Variability in weight in HF patients

Amongst the 1361 patients (92%) with three or more weight measurements during the first year of follow up, the median standard deviation in weight was 2.2 kg (IQR: 1.2-3.5). There was no difference in the variability of weight amongst patients between the different beta-blocker therapy groups. (Table 1) Patients with BMI ≥ 30 had the greatest variability in body weight compared to patients in other BMI categories. (Appendix 3)

Prognostic importance of weight change, baseline BMI and beta-blocker therapy

Patients were followed from the end of the first year onward. During a median subsequent follow up of 1876 days (interquartile range: 993-3052 days), 894 (60%) patients died. Univariable and multivariable predictors of mortality are shown in Table 2. In univariable analysis, increasing BMI, significant weight gain and beta-blocker therapy were associated with a better outcome. In multivariable analysis, the development of cachexia and the absence of beta-blocker therapy were independently associated with increasing all-cause mortality.

Kaplan-Meier curves for the relationship between weight change, beta-blocker therapy and outcome are shown in Figures 1a and 1b. Compared to patients with significant weight gain, those who developed cachexia had a 60% higher risk of all-cause death. (Figure 1a) Compared to patients who had beta-blocker therapy at baseline and 1 year, those who did not have beta-blocker therapy at both time points had a 90% higher risk of all-cause death. (Figure 1b)

Tables 3a and 3b show the 1 year and 5 year mortality rates for patients divided by category of weight change, BMI and beta-blocker therapy. Patients with CHF who had the following 3

features: beta-blocker therapy both at baseline and 1 year, baseline BMI ≥25 and significant weight gain had the best outcome, while patients who did not have any of the above 3 features (i.e.no beta-blocker therapy at either time point; baseline BMI<25 and cachexia) had the worst outcome (1 year mortality: 2% vs 18%, 5 year mortality: 22% vs 73%) (Tables 3a-b).

Discussion

We found that amongst patients with CHF due to LVSD, those who were not receiving or were unable to take beta-blockers were more likely to develop cachexia and less likely to have significant weight gain than patients who received beta-blocker therapy. Significant weight gain and beta-blocker therapy were independently associated with improved survival. Our results are similar to those from the COPERNICUS trial, which studied 2289 patients with HF and left ventricular ejection fraction of <25%. Compared to patients randomised to placebo, those who received carvedilol were 33% less likely to become cachectic (weight loss of >6%) and 37% more likely to have a significant gain in weight (≥5%): these changes were associated with better outcome.[7]

It is difficult to dissect the exact causal explanation for these findings. The beneficial effects of beta-adrenergic blockade on cardiac cachexia might be related to the role of the sympathetic activation on the development of cardiac cachexia.[10] Patients with CHF have marked sympathetic activation; in particular cachectic patients have a higher level of circulating noradrenaline than non-cachectic patients with HF.[5]

Sympathetic activation might contribute to cachexia by increasing total body energy expenditure[11] and directly exerting a myotoxic effect on skeletal muscle.[12] It also inhibits the secretion of leptin,[13] stimulates release of pro-inflammatory cytokines[14] and the development of insulin resistance,[15] which can all lead to wasting of muscle and adipose cells.

Beta-blockade reduces total body resting energy expenditure and prevents catecholamine-induced myotoxicity. [16] Beta-blockade might also prevent weight loss by improving fatigue and exercise tolerance,[17] perhaps in association with improved appetite. Inhibition of the renin-angiotensin system in patients with heart failure by angiotensin converting enzyme inhibitors and angiotensin receptor blockers also reduces the likelihood of weight loss,[18,19] suggesting that there is a strong relation between neurohormonal activation and weight loss.

Although obesity is a risk factor for developing heart failure, once HF develops, a higher BMI is associated with better survival, a phenomenon sometimes called the obesity paradox. Current guidelines do not recommend weight loss in patients with CHF and BMI<35. [20,21] We have found that incident cachexia is more common in obese patients than normal weight patients. It is important to acknowledge that weight loss in obese patients carries a poor prognosis, even though weight loss might result in a body mass index still in the normal range.[22] Weight loss in an obese patient should trigger the same concern as weight loss in a patient with normal weight.

Limitations:

Our findings should be interpreted with caution for several reasons.

Firstly, the definition of cachexia is arbitrary, and might not be appropriate in all patients with CHF. Changes in weight following treatment, including beta-blockers, ACEi and diuretics, might be related to changes in fluid status rather than loss of muscle or fat mass. However, it would be highly unlikely that many ambulatory patients with CHF have substantial (>5% of body weight) fluid accumulation; we also found that weight loss between baseline and 1 year was correlated with worsening rather than improved oedema status.

Secondly, patients were enrolled between 2000 and 2016, and clinical practice has substantially changed over this period. We did not look at changes in the incidence of cachexia over time in our study. It is possible that the prevalence of cachexia is increasing as patients age and are at lower risk of sudden death compared to around 20 years ago.[23]

Thirdly, we cannot ascertain whether weight loss was intentional or unintentional and we did not collect information on whether weight loss occurred in the presence of concomitant comorbities, such as cancer, which would have contributed to incident cachexia, and worse outcome, at least in some.

Fourthly, we only analysed weight change during baseline and 1 year follow-up, and thus those who died within a year, or did not attend 1-year follow-up visit, were not included in the analysis. Moreover, we have no data on weight changes from 1 year to time of event.

Fifthly, the effect of beta-blockade on cachexia might be confounded by other factors, such as changes in other anti-HF medications or the use of cardiac resynchronisation therapy, both of which prevent weight loss in patients.[18]

Finally, this is a single observational study conducted in the UK; external validation of our results from other countries with different healthcare and social systems is needed.

Conclusion:

Around 13% of patients with CHF due to LVSD develop cachexia during one year follow up. Those who are not treated with beta-blockers are at higher risk of developing cachexia and have the worst survival. The findings support the role of sympathetic antagonism in the prevention of cachexia.

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Legends

Tables:

Table 1a. Baseline characteristics of patients with CHF according to beta-blocker treatment groups.

Table 1b: Baseline characteristics of patients with CHF according to categories of weight change.

Table 2: Univariate and multivariate analysis for predictors of mortality.

Table 3a: Percentage 1 year mortality according to categories of weight change, BMI and beta-blocker therapy.

Table 3b: Percentage 5 year mortality according to categories of weight change, BMI and beta-blocker therapy.

Figures:

Figure 1a: Kaplan meier cumulative survival curve according to categories of weight change in patients with CHF.

Figure 1b: Kaplan meier cumulative survival curve according to categories of beta-blocker therapy groups in patients with CHF.

Appendices:

Appendix 1: Recruitment of patients

Appendix 2a: Degree of weight change in patients with CHF according to beta-blocker therapy groups. The numbers within the bars represent the % of patients within each weight change category. P<0.001

Appendix 2b: Degree of weight change in patients with CHF according to baseline BMI groups. The numbers within the bars represent the % of patients within each weight change category. P<0.001

Appendix 3: Variability in weight in patients with CHF according to BMI categories.

