

Fat Malabsorption in Elderly Patients with Cardiac Cachexia

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Summary

Malnutrition resulting from chronic congestive heart failure (cardiac cachexia, CC) is not uncommon and contributes to mortality and morbidity especially of elderly people. The aetiology of cardiac cachexia is probably multifactorial. We have assessed whether malabsorption of fat is associated with CC and if so whether it is due to small-bowel bacterial overgrowth.

Three groups of subjects were studied: 29 (20 women) patients (mean age 76.1 years) with controlled congestive heart failure and weight loss (CC); 14 (seven women) patients (mean age 74.0 years) with controlled congestive heart failure and no weight loss (non-cachexia, NON-CC); and 29 (20 women) healthy controls (mean age 74.9 years).

Fat absorption was quantified using the cumulative 6 h ^{14}C exhalation in the ^{14}C -triolein breath test and small-bowel bacterial overgrowth was quantified using the cumulative 8 h ^{14}C exhalation in the ^{14}C -glycocholic acid breath test.

The cumulative 6 h ^{14}C exhalation in the triolein breath test was reduced in the CC group ($p = 0.001$) implying impaired fat absorption. There was no evidence of small-bowel bacterial overgrowth in any group. Impaired absorption of fat was related to the clinical severity of heart failure and its duration.

Impaired fat absorption is associated with cardiac cachexia. It is not due to small-bowel bacterial overgrowth. The aetiology of fat malabsorption in heart failure requires further studies.

Introduction

Cardiac cachexia is undernutrition developing as a consequence of chronic congestive heart failure (CHF) [1]. Undernutrition *per se* may affect cardiac structure, size and function leading to the 'cachectic heart' [2], thus instituting a vicious circle. Although cardiac cachexia was first described by Hippocrates [3] ('The flesh is consumed and becomes water . . . , the feet and legs swell, the shoulders, clavicles, chest and thighs melt away'), few have attempted to explore its pathogenesis [4, 5].

Undernutrition probably occurs in 50% of patients with chronic heart failure [6], but is often unrecognized because of heart failure oedema. It is more common in elderly patients because of the increased prevalence of CHF and undernutrition in this population [7]. The prevalence of CHF is 1% in the general population rising to 4% in those over 65 years [8]. Subnutrition probably affects 1-2% of the elderly population [9]. Congestive heart failure has a poor prognosis, only 50% of patients surviving 5 years after diagnosis [10]. Undernutrition itself is also associated with an increased mortality [11]. Hence the presence of both is frequently a lethal combination in older people [7]. An understanding of the underlying mechanisms of cardiac cachexia may allow the treatment of CHF and undernutrition independently thereby reducing

the excessive morbidity and mortality associated with this condition.

Fat malabsorption has been implicated in the development of cardiac cachexia [12-14] but the relevant studies were poorly designed and uncertainty still exists about the role of fat malabsorption in cardiac cachexia. We have measured fat absorption in elderly patients with cardiac cachexia using the ^{14}C -triolein breath test which is a convenient, sensitive and specific procedure [15]. Gut hypomotility in heart failure may result in a blind loop syndrome causing small-bowel bacterial overgrowth which has been shown to be an important cause of occult malabsorption in elderly patients even in the absence of anatomical abnormality [16]. This was also investigated using the ^{14}C -glycocholic-acid breath test [17].

Methods

Patients: Two groups of patients with congestive heart failure were studied: 29 (20 women) patients [mean age 76.1 (SD 4.4) years] with a documented weight loss of at least 6 kg in the preceding 12 months; and 14 (seven women) patients [mean age 74.0 (SD 4.3) years] who had a documented stable weight (± 1 kg) in the preceding 12 months. Severity of CHF was categorized according to the New York Heart Association (NYHA) classification. The aetiology of heart failure in each patient was recorded. All patients had had clinical evidence of left ventricular failure and a chest radiograph showing

pulmonary oedema at the time of initial diagnosis. Optimal medical control of the heart failure had been present for 12 months in all patients entered into the study. Entry criteria included absence of peripheral oedema and stable diuretic therapy over the preceding 12 months. Patients were excluded if they had any co-existent disease which might cause undernutrition in its own right (diabetes, thyrotoxicosis, cancer, gastrointestinal disease or surgery). Subjects with pulmonary disease were also excluded as this may independently affect the exhalation of $^{14}\text{CO}_2$.

Controls: Twenty-nine (20 women) healthy, elderly controls [mean age 74.9 (SD 4.8) years] were studied. They were recruited from GP registers and luncheon clubs. All were screened by clinical history and examination, baseline blood tests, chest radiography and ECG. All were healthy at the time of study, on no regular medication and did not have any relevant past medical history.

The study was approved by the Wirral District Ethics Committee and the Administration of Radioactive Substances Advisory Committee (ARSAC). All subjects gave informed consent to the procedures.

Anthropometric measurements: All measurements were performed by a single experienced observer (D.K.). Height (ht) (m) was measured without shoes to the nearest 0.5 cm. Weight (wt) (kg) was measured with the patient wearing underwear and a hospital gown to the nearest 0.1 kg using a beam balance. Body mass index (BMI) was derived as wt/ht^2 (kg/m^2). Skin-fold thickness was measured using Harpenden calipers in four areas: triceps (TS) (mm), biceps (BS) (mm), subscapular (SUS) (mm) and supra-iliac (SIS) (mm) to the nearest 0.5 mm. Mid-arm circumference (MAC) (cm) was measured using a plastic tape at the mid-point between the acromion and olecranon process to the nearest 0.1 cm. The mean of three measurements for skin-fold thickness and MAC was taken. Arm muscle circumference (AMC) (cm) was derived from the equation:

$$\text{AMC} = \text{MAC} - (\text{TS} \times 0.314).$$

Total body fat (TBF) and fat-free mass (FFM) were calculated using equations derived by Durnin and Wormersley [18].

All subjects were asked if their appetite was reduced over the preceding 12 months and whether they experienced epigastric fullness after relatively small amounts of food (early satiety).

Biochemistry: Fasting blood samples were taken for estimation of albumin (Alb), bilirubin (Bil), alkaline phosphatase (ALP), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), total protein (TP) and glucose (FBS) (Excel analyser, Indianapolis, USA), thyroid stimulating hormone (TSH) (immunoradiometric assay, IDS Ltd). All samples were analysed in one hospital laboratory.

^{14}C -Triolein breath test: After an overnight fast subjects ingested 0.2 MBq of ^{14}C -triolein (Amersham International, plc) suspended in 4 ml of olive oil with a test meal of 40 ml of calogen (Scientific Hospital Supplies, Liverpool). Calogen is a white emulsion containing long-chain triglycerides. Forty millilitres provides a standardized fat intake of 20 g which provides an optimal amount of $^{14}\text{CO}_2$ exhalation [15]. The subjects remained at rest throughout the 6 h study period during which hourly breath samples were taken. Results are expressed as 6 h cumulative $^{14}\text{CO}_2$ exhalation as a percentage of the ingested activity [19].

^{14}C -Glycocholic acid breath test: All subjects had not received antibiotics for 4 weeks prior to the test. After an overnight fast, subjects ingested 0.2 MBq of ^{14}C -glycocholic acid (Amersham International, plc) with a standard test meal of 300 ml casilan (Crookes Pharmaceuticals, Nottingham). Breath samples were collected as for the ^{14}C -triolein breath test for a total of 8 h. Results are expressed as 8 h cumulative $^{14}\text{CO}_2$ exhalation as a percentage of the ingested activity.

Analysis of breath tests: Expired $^{14}\text{CO}_2$ was collected through a calcium chloride column into a trapping agent consisting of 4 ml methylbenzethonium hydroxide and a pH colour indicator (thymolphthalein) [20]. When the indicator becomes colourless the solution is saturated and contains 0.45 mmol of CO_2 . Careful observation was required by a single worker (D.K.) to collect satisfactory samples and to prevent the subject sucking up the solution.

Scintillant (10 ml) was added to each sample vial from the subjects and a background vial and a standard vial containing a known amount of ^{14}C . All vials were prepared and counted in the liquid scintillation counter (LKB Wallac, Helsinki) by a single worker (T.J.C.). For calculation of the percentage of CO_2 exhaled/h, it is assumed that the production of CO_2 at rest is 9 mmol/kg/h.

Breath tests were performed at least 7 days apart. All tests were on an outpatient basis and no subject found the procedure uncomfortable.

Statistical analysis: Normality of distributions was confirmed using the Kolmogorov-Smirnov goodness-of-fit test. Non-normal data were normalized by logarithmic transformation (wt loss, Bil, AST, and GGT). Differences between groups were explored using Student's *t* test, ANOVA, Pearson's product moment correlation (r_p), Spearman's rank correlation (r_s) and χ^2 , as appropriate. Data are expressed as mean (SD).

Table 1. Clinical characteristics of patients with heart failure

	CC (n = 29)	NON-CC (n = 14)
Severity of heart failure NYHA		
II	9	8
III	15	6
IV	5	0
Rhythm		
SR	9	5
AF	20	9
Orthopnoea*		
Yes	27	4
No	2	10
Early satiety**		
Yes	20	2
No	9	12
Anorexia***		
Yes	13	1
No	16	13

CC = cardiac cachexia group; NON-CC = patients without cachexia.

* $p < 0.001$; ** $p < 0.01$; *** $p < 0.05$.

Table II. Aetiology of heart failure in subjects with (CC) and without (NON-CC) cardiac cachexia

	CC (n = 29)	NON-CC (n = 14)
Rheumatic heart disease	12	4
Idiopathic dilated cardiomyopathy	5	4
Ischaemic heart disease	4	3
Unknown	3	1
Atrial septal defect	2	0
Patent ductus arteriosus	1	0
Hypertension	2	1
Mitral valve prolapse	0	1

Results

The mean duration of heart failure was similar in each heart-failure group: 7.0 (8.5) (range 0.4–38) (CC) years and 7.4 (10.9) (range 0.3–40) (NON-CC) years. Average weight loss in the cachectic group in the preceding 12 months was 8.50 (3.2) kg. There was a relationship between weight loss and the duration of heart failure ($r_p = 0.41$, $p = 0.03$) but not its severity ($r_s = 0.09$, $p = 0.32$). The clinical characteristics and the aetiology of heart failure are summarized in Tables I and II. The heart failure groups differed in their symptomatology, the NON-CC group being no different from the controls in terms of anorexia ($\chi^2 = 0$, $p = 1$) and satiety ($\chi^2 = 1.72$, $p = 0.19$) (Table I). As expected, the CC group showed evidence of under-nutrition as compared with both the NON-CC group

Table III. Anthropometric and biochemical measurements [mean (SD)]

	Controls (n = 29)	CC (n = 29)	NON-CC (n = 14)
Weight (kg)*	67.5 (14.76)	51.8 (9.91)	70.2 (15.86)
MAC (cm)*	29.2 (3.34)	23.0 (2.05)	28.6 (3.52)
AMC (cm)**	21.7 (3.18)	19.7 (2.15)	23.0 (3.03)
TBF (kg)*	26.8 (7.92)	13.7 (3.23)	25.6 (8.38)
FFM (kg)	40.7 (9.69)	38.1 (8.72)	44.6 (10.51)
BMI (kg/m ²)*	25.3 (3.93)	19.6 (2.53)	26.3 (4.68)
Bil (μ mol/l)**	8.0 (1.40)	13.2 (2.32)	11.2 (1.61)
ALP (IU/l)***	96.5 (42.87)	145.7 (82.55)	109.7 (44.38)
AST (IU/l)***	18.4 (1.29)	24.8 (1.78)	25.8 (1.38)
GGT (IU/l)*	17.5 (1.62)	64.9 (2.48)	39.8 (1.80)
Alb (g/l)**	42.9 (2.48)	41.0 (4.09)	44.9 (3.52)

Analysis of variance: * $p < 0.001$; ** $p < 0.01$; *** $p < 0.05$. MAC, Mid-arm circumference; AMC, arm muscle circumference; TBF, total body fat; FFM, fat-free mass; BMI, body mass index; Bil, serum bilirubin; ALP, serum alkaline phosphatase; AST, serum aspartate aminotransferase; GGT, serum gamma glutamyltransferase; Alb, serum albumin.

Table IV. Cumulative ¹⁴C₂ exhalations (%) in the triolein (TBT) and glycocholic acid (GABT) breath tests [mean (SD)] in controls, and heart failure patients with (CC) and without (NON-CC) cardiac cachexia

	Controls (n = 29)	CC (n = 29)	NON-CC (n = 14)
TBT**	12.84 (7.22)	7.25 (3.61)	10.85 (4.71)
GABT*	3.9 (2.69)	3.34 (2.96)	6.49 (4.60)

Analysis of variance: ** $p = 0.001$; * $p = 0.02$.

and the control group (Table III). The CC group had significant lower values from all skin-fold thicknesses and a significantly lower total body fat.

¹⁴C-Triolein breath test: The CC group had a lower cumulative 6 h ¹⁴C₂ exhalation (Table IV, Figure 1) consistent with impaired fat absorption in the CC

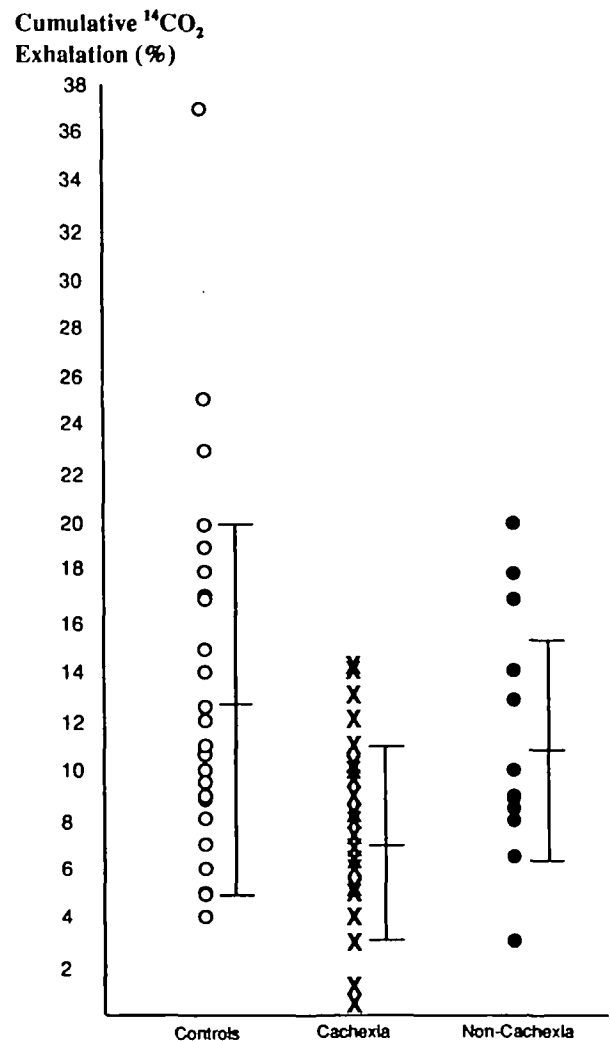


Figure 1. ¹⁴C-triolein breath test. All figures indicate mean with 1 SD error bars.

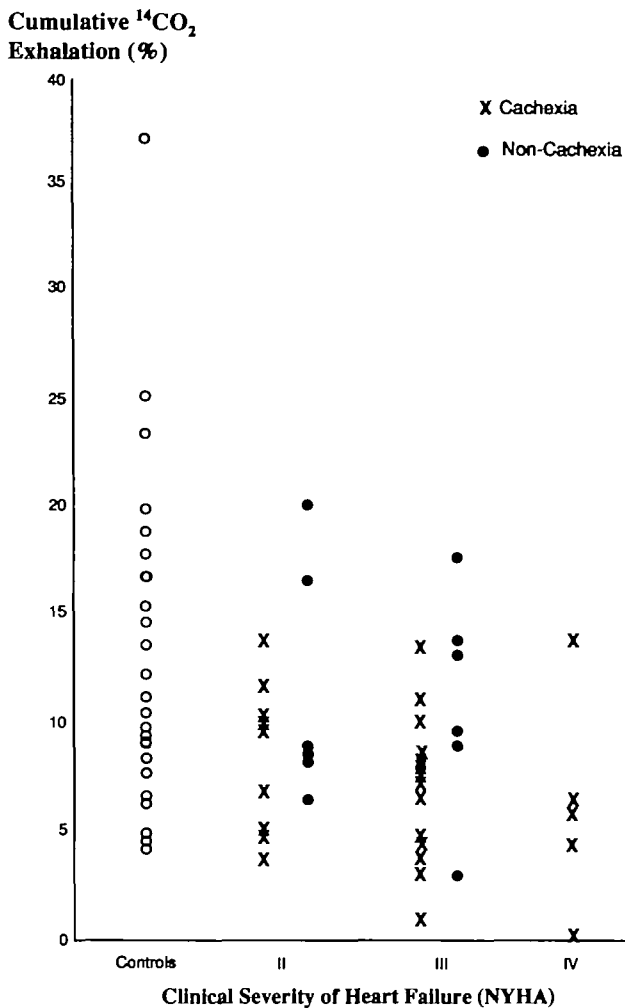


Figure 2. Relationship of ¹⁴C-triolein breath test to clinical severity of heart failure.

group with controls. There was no difference between the NON-CC and control groups. The rate of fat absorption was similar in all three groups. The peak ¹⁴CO₂ exhalation was seen in either the 5th or 6th hour in all groups but the hourly ¹⁴CO₂ values were less in the CC group. This therefore implies that there was quantitative fat malabsorption in the CC group rather than a delay in absorption. There was a correlation between ¹⁴CO₂ exhalation and severity of heart failure ($r_s = -0.37$, $p = 0.001$) (Figure 2) and also its duration ($r_p = -0.3$, $p = 0.05$) indicating impaired fat absorption in severe heart failure groups. There was an association between ¹⁴CO₂ exhalation and ALP ($r_p = -0.24$, $p = 0.04$) and GGT ($r_p = -0.33$, $p = 0.004$).

¹⁴C-Glycocholic-acid breath test: The cumulative 8 h ¹⁴CO₂ exhalation in the ¹⁴C-glycocholic-acid breath test was similar in the controls and CC (Table IV, Figure 3) but was higher in the NON-CC group. This difference was due to a single high value (20.05%).

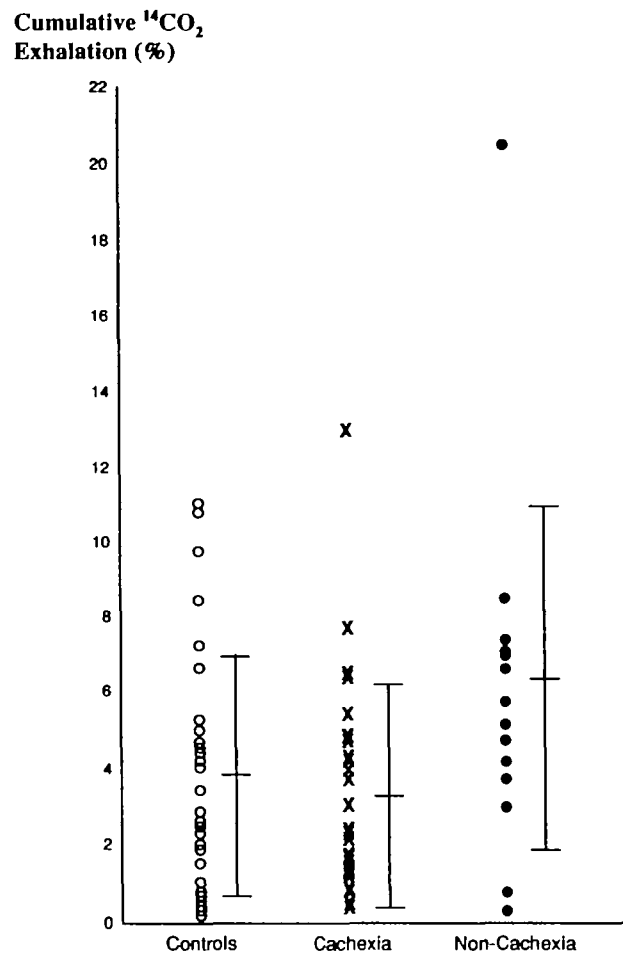


Figure 3. ¹⁴C-glycocholic acid breath test. All figures indicate mean with 1 SD error bars.

This patient had no evidence of fat malabsorption as measured by the triolein breath test.

Discussion

Fat malabsorption has previously been described as one of the underlying mechanisms in cardiac cachexia [12–14]. Those studies have demonstrated fat malabsorption using the ¹³¹I-triolein test. Vaughan Jones [12] also measured faecal fat excretion but in an uncontrolled study of patients with decompensated CHF which in itself might cause malabsorption. Although the other two studies [13, 14] were controlled, patients were in severe decompensated heart failure. Instability of the ¹³¹I label in the triolein test has resulted in false negatives [21]. Faecal fat estimation is also potentially unreliable as it is dependent upon a high fat diet which cannot always be tolerated by an anorexic patient. That test is further complicated by the need for a complete stool collection.

In the current study we have demonstrated relative fat malabsorption in undernourished patients with compensated CHF using a sensitive and specific test

[15, 19]. Faecal fat estimation was not performed, as a high-fat diet could not be tolerated by the CC patients and collection of faeces is unreliable. The ^{14}C -triolein breath test has been shown to have a high predictive accuracy for fat malabsorption [19]. In one study complete discrimination between controls and patients with steatorrhoea was shown with a sensitivity of 85% and a specificity of 93% [22]. The ^{14}C -triolein breath test can therefore be used reliably to replace faecal fat estimation as an index of malabsorption [23].

Our patients with cardiac cachexia experienced clinical problems of atrial fibrillation, orthopnoea, early satiety and anorexia significantly more frequently than both the NON-CC and control groups. It is not clear whether the symptoms of anorexia and early satiety are secondary to the increased prevalence of orthopnoea and atrial fibrillation in the CC group which might of themselves lead to decreased calorie intake and undernutrition, or whether these symptoms are related to a malabsorption syndrome in the cachectic group. Clearly a reduced intake of calories in patients with cardiac cachexia also contributes to undernutrition and this is the subject of another study. Previous studies [12–14] stated that fat malabsorption seemed to be worse in severe heart failure. We have now quantified this relationship using the New York Heart Association classification for functional capacity in heart failure. We have also demonstrated a relationship between fat malabsorption and duration of heart failure.

Fat absorption is a complex process [24] involving the hydrolysis of dietary triglyceride by pancreatic lipase. The resulting fatty acids and monoglycerides combine with bile salts to form micelles which are then absorbed across the mucous membrane into the intestinal cell where triglycerides are resynthesized and incorporated into chylomicrons before being transferred into the lymphatic system. A defect at any of these stages may result in malabsorption of fat.

Patients with CHF often have abnormal liver function [25, 26] as seen in the present study. This could theoretically result in decreased production of bile salts and consequent fat malabsorption. Although we have shown a relationship between ALP and GGT and fat malabsorption, the functional capacity of the liver does not seem to have been impaired as demonstrated by the normal serum albumin in all the groups in this study.

Bacterial colonization of the small bowel may cause fat malabsorption by the deconjugation of bile acids even in the absence of a blind loop [27]. We did not find evidence of bacterial overgrowth in this study.

Fat malabsorption appears to be one factor in the production of cardiac cachexia. The mechanism of this malabsorption is likely to be complex and further work looking at each step of the process is required. Appreciation of the mechanism of fat malabsorption in patients with cardiac cachexia could result in specific treatment with the consequent improvement of the

high morbidity and mortality associated with this common condition.

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