Cardiac cachexia in early literature: a review of research prior to Medline

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ABSTRACT | Cachexia has been known to physicians since ancient Greek times as a 'signum mali ominis' in various diseases indicating end stage disease and poor quality of life. Cardiac cachexia is recently receiving growing attention as modern treatment options prevent early death from cardiac events and more patients live with chronic compensated heart failure. Nevertheless, observation and clinical documentation of this condition go back as long as medical science itself. Pioneering studies on the reasons and mechanisms of cachexia were performed several decades ago. These studies provide fundamental insights and guidance towards a better understanding of cachexia. This review presents an overview of early thoughts and milestone studies on metabolic abnormalities and cachexia in chronic heart failure.

KEYWORDS | Cachexia; Metabolic abnormalities; Chronic heart failure; History.

1. Introduction

Heart disease is today in the centre of medical attention. Within the last 50 years, therapeutic options have improved greatly. Since the introduction of the first mercury diuretics, the control of fluid balance became a cornerstone for cardiac therapy. Antibiotics, from the beginning, have been used to ameliorate deleterious effects of infections causing and/or aggravating valvular diseases. With increasing insight in the complex pathophysiology of the cardiovascular system, both powerful medical and interventional therapeutical options are now in our hands for the treatment of cardiac disease. As a result, fewer people die from an acute cardiac event or early in a decompensated state and an increasing number of patients are seen with longer lasting, compensated chronic heart failure. New problems emerged with this shift in the patient population and complications of late stage chronic heart failure are of rising importance. Cardiac cachexia is therefore increasingly recognised and the research interest in this complication of chronic heart failure is growing [1]. Cachexia is known to physicians for centuries as a 'signum mali ominis' indicating end stage disease and poor quality of life. Cardiac cachexia has been recognised by doctors in all times and early annotations can be found in the medical literature dating back as long as medical science itself.

In this review we present a historic overview on cardiac cachexia from the first anecdotal documentation to the beginning of its systematic investigation. The material reviewed in the following is taken entirely from Western sources. We concentrated on material that was published prior to the start of the online library Medline and is mainly based on the Index Medicus which dates back as far as the 18th century (►Fig. 1).

2. Early annotations

The earliest report on significant weight loss in relation to what can be diagnosed as heart failure dates back 2400 years to classical Greece and the school of medicine of Hippocrates (about 460–377 BC) on the island of Cos. Observing an association between dropsy and cachexia, Hippocrates wrote that 'the flesh is consumed and becomes water,… the abdomen fills with water, the feet and legs swell, the shoulders, clavicles, chest and thighs melt away… This illness is fatal' [2]. Hippocrates also recognised the severely impaired prognosis of this syndrome. The origin of the term 'cardiac cachexia' is also Greek: derived from the words *kakós* (i.e. bad) and *hexis* (i.e. condition or appearance). It was, however, to be established only many centuries later as no understanding of the physiology of the heart and the circulatory system existed in ancient Greece and the heart was in fact debated as being the location for the intellect. Regardless of the lack of understanding of the underlying reasons, these passages in the corpus Hippocratus provide almost the only high quality clinical records on cachexia for the next 1700 years.

When the term cardiac cachexia was first introduced into medical literature remains uncertain. The understanding of the physiological function of the heart was of course a prerequisite. In 1628 Harvey discovered the circulatory physiology and recognised the heart rightly

as the driving pump for the circular movement of the blood [3]. This finding replaced the then prevailing Galenic view of the heart generating and distributing *pneuma* and heat throughout the body [4]. Only now it was possible to link symptoms of a failing circulation with pathophysiological findings of the heart. A rather anecdotal case of what likely was cardiac cachexia was observed by Withering (1741–1799) in 1785. In his work 'An Account of the Foxglove and some of its Medical Uses with Practical Remarks on Dropsy and other diseases' (which was to introduce digitalis into modern medicine) he wrote about one of his patients '…his countenance was pale, his pulse quick and feeble, his body greatly emaciated, except his belly, which was very large' [5]. The earliest written documentation of the term cardiac cachexia comes from Charles Mauriac, a French Physician. In his medical thesis, in 1860 he wrote of a 'commonly observed secondary phenomenon in patients affected with diseases of the heart… a peculiar state of cachexia which is …conventionally designated cardiac cachexia' [6]. Similar observations were reported by others: 'Disease of the heart occasionally results in a certain picture of cachexia 'Chachéxie cardiaque' due to blood congestion etc. The 'heart failure colour' of some heart patients is known; a distinct livid paleness is indicative in many heart patients' [7].

Apart from these rare reports, cardiac cachexia as a syndrome was not studied in much detail by clinical scientists for many years to come. If recorded, authors mostly did not extend their reports beyond the state of mere observation. Anorexia was known to accompany cardiac decompensation and the grave prognosis in those cases was well recognised. '…But other cases occur which are neither so frequent nor so well known; in these the exertion does not give rise to sudden death, but starts a slowly ingravescent asthenia from which there is no recovery' [8]. However, potential mechanisms for this have not been explored in detail. Weakness and a reduced urge to eat were easily accepted as underlying mechanisms of weight loss.

To understand the lack of interest in this syndrome it has to be viewed in the context and the background of the clinical setting in the 19th and the beginning of the 20th century. Cachexia was of course known to physicians as a severe clinical condition indicating both grossly reduced life quality and early death. It was, however, seen more in the context of diseases other than the failing heart, mainly in relation to severe undernutrition or as a very serious complication in diseases like tuberculosis, malignancies or uncontrolled metabolic disorders like diabetes mellitus or thyreotoxicosis. In comparison to those diseases, cardiac cachexia was a rather rare condition, simply because the vast majority of patients with heart failure would not reach the state of chronicity for cachexia to develop. No sufficient and practicable treatment to control for fluid overload was available and heart failure patients—mostly with valve diseases as the underlying aetiology—died early in the course of the disease in a state of acute decompensation. With the introduction of modern therapy it was possible to keep patients in stable, compensated condition for longer time periods. Only then have the lives of patients suffering from various forms of heart disease been prolonged considerably, and consequently new aspects of the disease emerged with the extended duration of the disease including a growing number of patients with cardiac cachexia. A shift in the perception of the disease occurred which is also expressed by the gradual change from the term congestive heart failure to the more commonly-used term chronic heart failure or chronic congestive heart failure in today's literature.

3. Franklin D Roosevelt: a case of cardiac cachexia

The following case may illustrate that, beside the personal tragedy, fundamental historical implications may arise from certain cases of cardiac cachexia. When Franklin D. Roosevelt became President of the United States in 1935, he had been profoundly affected by poliomyelitis and he suffered from persistent hypertension. He was also being treated with digitalis for congestive heart failure. Shortly before the Yalta Conference (February 1945), it became evident that he had developed cardiac cachexia leaving the President with increasing weakness and fatigue at minimum exertion [9]. In their conference on post-war strategies for Europe, Churchill and Stalin were able to take advantage of Roosevelt's poor health status. It has been commented that '…at the Conference, Roosevelt's cerebral arteriosclerosis and reno-vascular hypertension and cardiac cachexia certainly affected his judgment, leading to the imposition of communism in Eastern Europe and Asia' [10]. Thus, Roosevelt's cardiac cachexia profoundly affected the outcome of the Yalta meeting, and the course of world history for the following decades. We are interested to learn more about famous cases of cardiac cachexia, and we would be happy if any reader with such information contacted us.

4. Pioneering studies

The observation of major alterations in body composition that accompany chronic heart failure has been attributed commonly to anorexia, i.e. reduced eating. Voluntary reduction of food intake was even seen as a compensatory mechanism, to prevent the additional strain, that a large meal with the resulting increase in splanchnic blood flow may impose on the weak heart [11]. 'The histories leave no doubt that anorexia is the chief cause of the malnutrition (in congestive heart failure), with nausea and vomiting frequently acting as contributory factors' [12]. Although this view was widely accepted, quantitative data derived from balance studies are rare. In a small study on decompensated heart failure patients with anorexia, a negative nitrogen and caloric balance was found which became positive with recompensation and a voluntary increase in food intake [13]. The situation for patients with cardiac cachexia might have been worsened by the fact that often the caloric intake was further reduced by dietary restrictions imposed on any patient with heart failure by the physicians of that time. A restricted diet was widely accepted as beneficial for the 'senile' heart [14] and a variety of diets existed for that purpose. For example, the Karrel diet [15] was very popular for several decades, however—although salt restriction was a desired side effect—the 800 ml milk and nothing else that comprised Karrel's prescription was less than satisfactory.

Prospective studies on mechanisms of cardiac cachexia were rare in the first half of the 20th century for the reasons given above. There was, however, pioneering work done that provided the foundation for today's knowledge of the pathophysiology of cardiac cachexia. Some of the current theories have their roots in the work that was done decades ago (▶Table1), like for instance studies on hypoxia [16], subacute inflammation in HF [17] or upregulated sympathetic activation [18].

Several studies have shown a connection between cardiac congestion and impaired intestinal capacity for absorption of nutrients. As early as 1888 it was shown that in patients with congestive heart failure due to valvular defects, impairment of intestinal absorption can be measured. In this study, fat absorption was reduced by 18% whereas nitrogen and carbohydrate absorption were only marginally impaired [19]. This is very similar to what has been described by King et al. in two studies 107 years later [20 and 21]. In 1938 an Italian group found increased steatorrhea in 12 of 20 cases with oedematous cardiac patients [22]. In the early

1960s several studies using I^{131}-labelled fat administration gave further evidence of reduced fat absorption in congestive heat failure [23 and 24]. The authors noted a correlation between severity of the congestion and the degree of steatorrhea as well as a reversion to normal fat absorption when compensation could be achieved. Those studies were based on the hypothesis that elevated venous pressure may cause congestive oedema of the intestinal wall which was indeed reported in 1943 [25]. Also, abnormal protein absorption was reported for heart failure patients with the finding of protein-losing gastroenteropathy [26] contributing to reduced oncotic pressure and the production of cardiac oedema and impaired intestinal absorption of amino acids in oedematous patients [27].

Already at the beginning of the 19th century, physicians noted an important factor in the wasting process in chronic heart failure that could not be explained by simple reduction of caloric intake. It may serve as an example for the observational skills of these physicians that was the basis for many discoveries in times when today's technology was not available: in contrast to uncomplicated starvation, where the energy expenditure is compensatorily decreased, an elevated metabolic rate was recognised in patients with heart failure. Several symptoms like tachycardia, hyperpnea, sweating and a rise in body temperature indicated an increase of the metabolic rate that stands in sharp contrast to the reduced energy supply in these patients [28]. In 1916, the increase in the basal metabolic rate was directly documented [29 and 30]. Increased metabolic demands of several specific tissues were discussed as one underlying reason for this finding. Decreased efficiency of the respiratory system due to reduced compliance [31] and capacity of the lungs together with hyperventilation result in higher energy demands of the respiratory muscles [32]. It was also suggested that the hypertrophied myocardium may contribute to the hypermetabolism in chronic heart failure [33 and 34]. The combination of an increase in total energy consumption of the heart and reduced cardiac output [35] was viewed as diminished myocardial efficiency [36]. Enhanced erythropoietic activity and hyperplasia of red bone marrow has also been repeatedly demonstrated [37 and 38] and was also discussed to contribute to increased caloric turnover.

In contrast to the increased metabolic demands of specific tissues, other abnormalities may produce a more generalised caloric effect. In this context, detailed studies revealed that elevated body temperature is a common finding in patients with

chronic heart failure. In two large studies in the 1930s, the majority of patients with HF was found to have at least mildly elevated body temperature. In 1934, Cohen and Steel studied 300 cardiac patients for body temperature, measured rectal on two or more occasions [17]. In 172 of these patients heart failure was diagnosed. In this study, only 11% of the patients with heart failure had normal temperature but 89% had some degree of pyrexia. This came often from pneumonia or other infections. Other causes of inflammation, like thrombosis, pulmonal or myocardial infarctions, rheumatic activity and bacterial endocarditis were also diagnosed. Cohn and Steel also described a number of cases where the origin of the fever could not be established, mainly in those cases where temperature was only slightly elevated. In another study by Kinsey and White, out of 200 patients only four were free of fever [39]. Inflammatory immune activation may have been the cause for the fever. Today, one hypothesis suggests that bowel wall oedema causes bacterial translocation [40] which may explain increased levels of endotoxin that are found in decompensated heart failure patients [41].

Already back in 1934, Cohn and Steel discussed the possibility of a yet unidentified pyrogen causing the higher temperature [17]. The accuracy and thoughtful interpretation of these old studies is stunning in the light of the more recent finding of mild but measurable immune activation in patients with chronic heart failure characterised by elevated TNF-alpha levels and other pro-inflammatory cytokines [42 and 43].

The observation of constant 'air hunger' directed some research attention to the role of reduced oxygen supply to the tissue. The subject of cellular hypoxia became a focus of metabolic research already at the beginning of the 20th century. First blood gas analyses were reported as early as 1919 [16], and in 1923 it was observed in studies at high altitudes that in thin air, study subjects would involuntarily lose weight [44]. Evidence for reduced tissue oxygen supply came mostly from indirect observations like increased erythropoietic activity and elevated lactate production. Increased lactate levels as a measure of an imbalance between aerobic and anaerobic metabolism were reported in the 1930s and repeatedly thereafter [45]. In 1958, Huckabee introduced the concept of 'excess lactate' production as a measure of tissue hypoxia [46]. It was estimated that in heart failure 25 to 50% of the body's energy needs would be derived from anaerobic glycolysis [47]. In normal subjects, this study found that the anaerobic pathway would account for only 5% of the energy production during exercise. Those observations suggested

that lack of oxygen at tissue levels reduces energetic efficiency but also negatively affects protein biosynthesis leading to down-regulated anabolic and increased catabolic pathways.

Based on early observations of sweating, tachycardia, venoconstriction and systemic increased vascular resistance with reduced cutaneous and renal blood flow, an overactivity of the sympathetic nervous system was recognised. The finding of elevated norepinephrine levels in chronic heart failure patients by Chidsey et al. in 1962 supported this hypothesis [18]. The authors recognised this as compensatory mechanism to improve cardiac performance.

5. A complex picture emerges

More work was done in the 1950s and 1960s to study special aspects of metabolic malfunction and altered body composition secondary to chronic heart failure. The evidence emerging from these studies made it apparent that multiple mechanisms act in combination forming a complex web of metabolic imbalance with catabolism dominating the anabolic drive and the consequence of weight loss. A first attempt for a comprehensive overview on the complex pathophysiology of cardiac cachexia was made by Pittman and Cohen in 1965 [48 and 49] (►Fig. 2). From their review of related studies, they addressed three main pathophysiologic mechanisms of cardiac cachexia:

1. dietary factors,

2. loss of potential nutrients, and

3. abnormal metabolism of ingested food.

To briefly summarise the findings of Pittman and Cohen: dietary factors, i.e. reduced supply of nutrients to the body, as discussed before, are generally accepted as a factor of primary importance in the genesis of cardiac cachexia. Many reasons for a reduced food intake in the setting of reduced cardiac function have been discussed. Patients frequently complain of gastrointestinal problems and a whole range of reasons were identified: reduced gastric motility, delayed gastric emptying, a reduced capacity due to hepatomegaly, ascites, meteorism and pain due to distension or splanchnic angina. Also, psychological factors may account for reduced eating, like depression, fear of increased discomfort after a meal. In this context, also a change in the pattern of eating was discussed. Instead of eating a full meal three times per day, patients would start to eat small portions of food irregularly over long periods of the day. This 'nibbling' instead of the normal 'gorging' has been

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suggested to affect the intermediary metabolism and make the calorie uptake less efficient [50 and 51]. An excessive loss of potential nutrients due to impaired absorption or excessive excretion has been shown for fat as well as for protein absorption and vitamins [52].

At the same time, an increased metabolic rate due to increased energetic demands of specific tissues and generalised caloric factors like increased body temperature may further contribute to an unfavourable balance of the body's energy metabolism. As a result the catabolic drive may chronically dominate the anabolic pathways. The constant drain of the body's energy reserves may eventually lead to a pathological degree of tissue degradation.

More than a century of studying the phenomenon of cardiac cachexia has passed. Especially in the last decade, many specific aspects of this complication of chronic heart failure have been discovered [1]. The 19th century brought the medical term and the clinical recognition of cardiac cachexia, the 20th century focused on more sophisticated pathophysiologic studies of this subject. With regard to therapeutical options, however, cardiac cachexia still is an unknown and unconquered territory. In 1964 Pittman and Cohen conclude: 'Besides the avoidance of… potentially harmful forms of therapy, the only known treatment of cardiac cachexia requires improvement in cardiac function' [48]. This has not been amended until today. We believe, the 21st century will see this therapy being developed.

Acknowledgements

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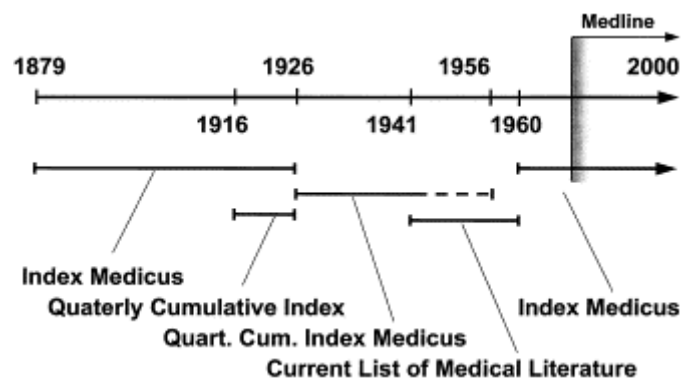
►Fig.1. Timetable of printed indices for medical publications from the beginning until the start of the computerized online library Medline.
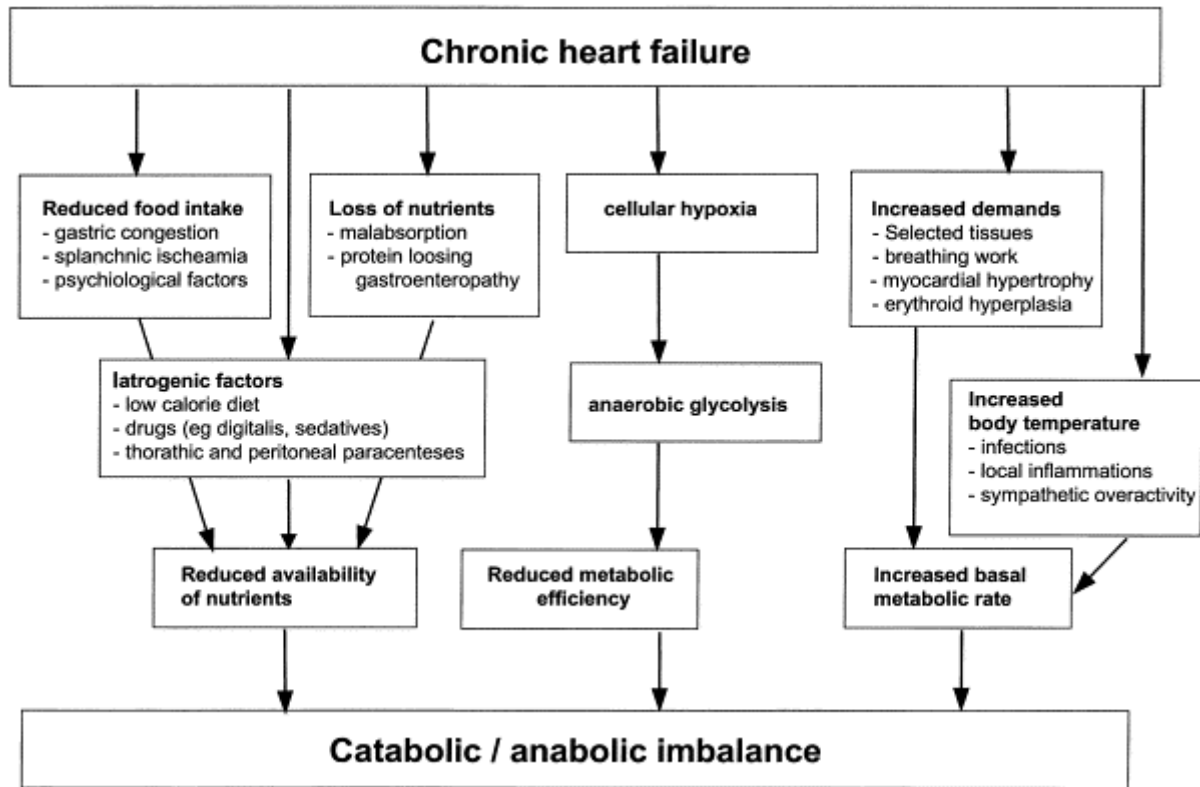
►Fig.2. Overview of the pathophysiologic mechanisms contributing to cardiac cachexia as suggested by Pittman and Cohen [48].

ca 400 BC	First observation of wasting realted with heart disease	Hippocratus, Hippocratic Corpus ca 400 BC
1860	First documented reference of cardiac cachexia	Mauriac C, Essai sur les maladies de cœur. Paris: L. Leclerc, 1860.
1888	Malabsorption in patients with cardiac disease	Grassmann, Zeitschr F Klin Med 1888; 15: 183-207.
1916	Elevated basal metabolism in cardiac failure	Peabody FW et al., Arch Int Med 1916; 17: 980-1009.
1923	Hypoxia is related to weight loss	Barcroft J, Cambridge University Press 1923: 190.
1932	Hypoalbuminaemia relates to anorexia in heart failure	Payne SA and Peters JP, J Clin Invest 1932; 11: 103-112.
1934	Occurrence of unexplained fever in congestive HF due to "pyrogens"	Cohn AE and Steele JM, J Clin Invest; 1934; 13: 853-868.
1935	Elevated lactate production in congestive HF	Weiss S and Ellis LB, Arch Int Med 1935; 55: 665-680.
1938	Fat malabsorption in decompensated heart failure patients	Bologna A and Castadoni A, Arch Ital de Mal d App digest 1938; 7: 215-254.
1958	Negative nitrogen and caloric balance in oedematous HF	Jaenike JR and Waterhouse C, J Lab Clin Med 1958; 52: 384-393.
1962	Augmented sympathetic stimulation in congestive HF	Chidsey CA, Harison DC and Braunwald E, New Eng J Med 1962; 267: 650-654.

▶Table 1. Milestones in CHF/metabolic research