

Diabetes mellitus, cachexia and obesity in heart failure: rationale and design of the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF)

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Abstract

Background Chronic heart failure (CHF) is increasing in prevalence. Patients with CHF usually have co-morbid conditions, but these have been subjected to little research and consequently there is a paucity of guidance on how to manage them. Obesity and diabetes mellitus are common antecedents of CHF and often complicate management and influence outcome. Cachexia is an ominous and often missed sign in patients with CHF.

Methods This manuscript describes the rationale and the design of Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF), a prospective, multicentre, multinational, longitudinal, pathophysiological evaluation

study, which is being conducted in 11 centres across six countries in the European Union and in Russia. We aim to recruit >1,600 patients with CHF due to various common aetiologies, irrespective of left ventricular ejection fraction, and with or without co-morbidities at study entry. In addition, >300 patients with type 2 diabetes mellitus without CHF and >150 healthy subjects will serve as control groups. Participants will be systematically investigated at annual intervals for up to 48 months. Additional investigations focusing on cellular and subcellular mechanisms, adipose and skeletal muscle tissue, and in endothelial progenitor cells will be performed in selected subgroups.

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Conclusions SICA-HF will provide insights into common co-morbidities in CHF with a specific emphasis on diabetes mellitus and body mass. This will provide a more thorough pathophysiological understanding of the complexity of CHF that will help develop therapies tailored to manage specific co-morbidities.

Keywords Heart failure · Pathophysiology · Diabetes mellitus · Obesity · Cachexia

1 Introduction

Chronic heart failure (CHF) poses a massive clinical, social and economic problem. It has been estimated that approximately 14 million people are affected in the European Union [1] and 5 million in the United States [2]. The average survival in epidemiological representative patient cohorts may be as poor as 3 years, suggesting that there may be >2 million new cases of heart failure in the European Union alone each year. Although there have been significant advances in the treatment of the disease over the last 20 years, CHF is still not curable, despite treatment aimed at limiting its progression [1, 2]. Altogether, the treatment of CHF consumes a greater percentage of healthcare costs than human immunodeficiency virus infection or cancer [3–5]. The last several years have seen growing research interest into subgroups of patients with the disease who are deemed to benefit from tailored therapies. This is particularly true for patients who have CHF and co-morbidities such as anaemia [6], renal failure [7], catabolic/anabolic imbalance [8] or atrial fibrillation [9]. In addition, dyssynchrony has recently received increasing research interest [10, 11].

Patients with CHF have different phenotypes, and those with left ventricular systolic dysfunction due to ischemic heart disease have been most intensively investigated [1, 2]; however, they represent <50% of patients managed in everyday practice [12, 13], and thus we still do not have sufficient insight into disease mechanisms, natural course and management of the majority of patients with CHF. There are several subgroups of patients with CHF that have received little systematic research so far. This particularly holds true for patients at the extreme ends of the body weight spectrum, i.e. patients with cardiac cachexia or obesity, as well as patients with type 2 diabetes mellitus. They have, so far, been treated as if their co-morbidities were not present, and current guidelines do not differentiate between such subgroups. A thorough understanding of the pathophysiological processes could hold the key to improve their management.

The importance of cardiac cachexia has long been underestimated in clinical practice [14]. Among 171 unselected patients with CHF, mortality rates were as high as 50% in the cachectic subset compared to 17% in the non-cachectic subset at 18 months of follow-up [15]. Overall, there is a scarcity of data on the prevalence and incidence of cachexia and obesity in patients with CHF, and only small studies have been reported so far [16]. In contrast with the widely accepted public belief that obesity shortens life expectancy, patients with CHF and a higher body mass index (BMI) may have better outcomes compared to those with a “normal” BMI in terms of a decreased risk of death and hospitalisation. This so-called “obesity paradox” has been shown in several databases of CHF [16, 17] and other cardiovascular diseases [18, 19], but no prospective data are available so far.

Overt diabetes mellitus is another common co-morbidity in patients with CHF, and the EuroHeart Failure Survey reported an incidence as high as 27% [20]. The prevalence of this co-morbidity ranges between 20% and 30% in prospective large-scale studies of ambulatory heart failure [21, 22], and elevated levels of glycated haemoglobin have been shown to be strong predictors of mortality among patients with heart failure [23]. Even less is known about insulin resistance, which also is common and predicts a worse prognosis [23, 24].

Little is known about the characteristics of these subgroups of CHF patients or about the effects of physical exercise [25], nutrition [26, 27] or drug therapies [28] on them. Neither do we know much about differences in commonly used biomarkers such as N-terminal pro-B-type natriuretic peptide nor about the effects of co-morbidities on measures of cardiac function such as left ventricular ejection fraction, cardiac output, exercise capacity and cardiorespiratory reflex control. The interplay between skeletal muscle, adipose tissue and other tissues or the

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pathophysiology of the responsible mediators is poorly researched.

The paucity of data with regard to heart failure and its co-morbidities and between the interplay of different tissues in this clinical syndrome has led to the design of the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF). This article gives details about the rationale, design and methodology of SICA-HF.

2 Methods

2.1 Study design

SICA-HF is a prospective, multicentre, multinational, longitudinal, pathophysiological evaluation study, which is being conducted in 11 centres across six countries. SICA-HF receives funding from the European commission's Seventh Framework Programme (FP7/2007–2013) under grant agreement no. 241558 (SICA-HF) and from the Russian Ministry of Science and Education within the FTP "R&D in priority fields of the S&T complex of Russia 2007–2012" under state contract number 02.527.11.0007. The participating centres are shown in Fig. 1; the study design is summarised in Fig. 2. The study is conducted in accordance with the Declaration of Helsinki principles and local/national regulations. National and/or local ethics

committees revised and approved the study protocol. A patient's written informed consent is mandatory prior to inclusion and any study-related procedure.

2.2 Eligibility

At baseline, patients will be screened for inclusion into the study. The aim of SICA-HF is to include a broad range of patients with CHF with or without co-morbidities at study entry. Both patients with preserved or reduced ejection fraction are eligible. Patients of any aetiology of CHF can be enrolled into SICA-HF. The inclusion/exclusion criteria as specified in Table 1 reflect these concepts.

2.3 Planned clinical investigations and follow-up

SICA-HF aims to recruit >1,600 patients with CHF. In addition, we will enrol subjects into two control groups, >300 patients with type 2 diabetes mellitus without CHF but at risk of developing heart failure and >150 healthy subjects without obvious risk of developing heart failure. All subjects will undergo a systematic cardiological evaluation, including echocardiography, resting electrocardiogram, full blood count and routine biochemistry analysis. Subjects will undergo a thorough clinical examination as detailed below. In addition, we aim to harvest adipose tissue samples, skeletal muscle and bone marrow



Fig. 1 Participating centres in SICA-HF

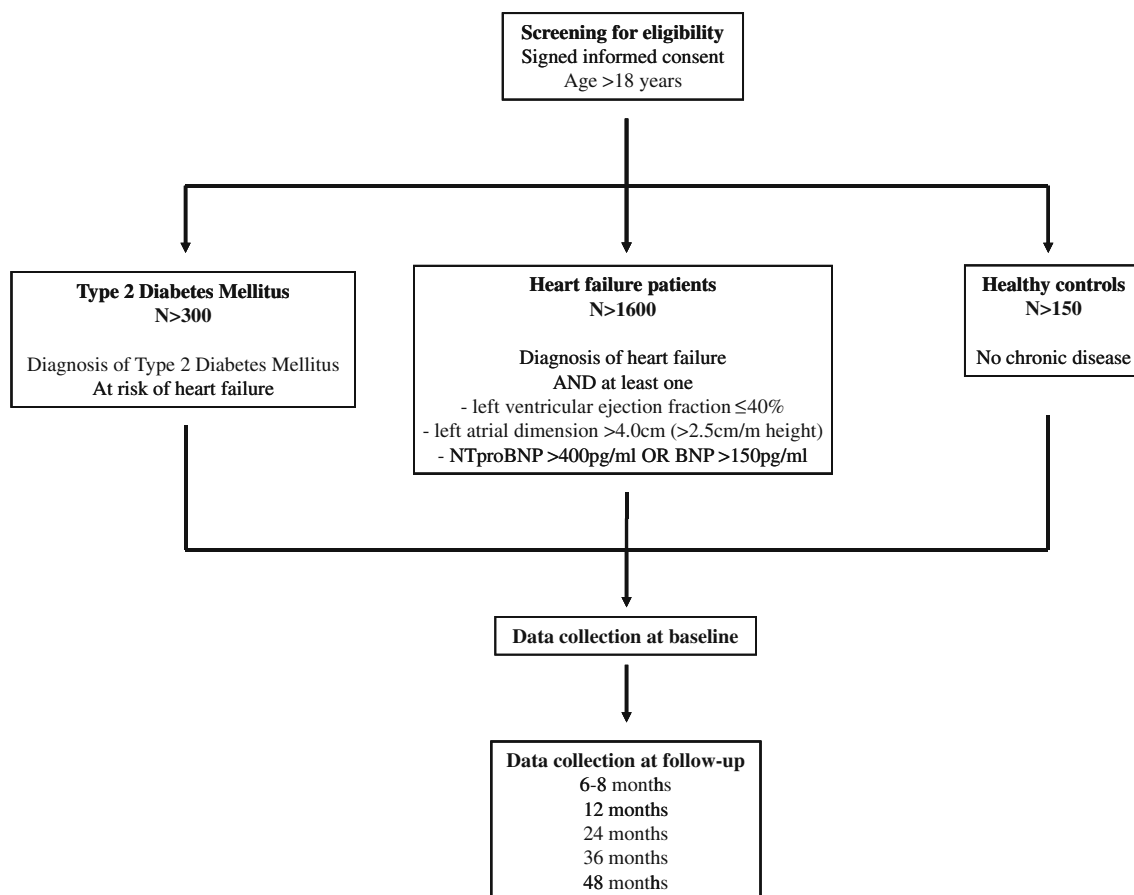


Fig. 2 Overview of SICA-HF

Table 1 Inclusion and exclusion criteria of SICA-HF

Inclusion criteria:

- Clinical diagnosis of heart failure
- Objective evidence of cardiac dysfunction as evidenced by at least one of the following:
 - Left ventricular ejection fraction $\leq 40\%$
 - Left atrial dimension >4.0 cm (or >2.5 cm/m in height)
 - NT-proBNP >400 pg/ml (>47.3 pmol/l) (or BNP >150 pg/ml)
- Age >18 years
- Willingness to provide informed consent

Exclusion criteria:

- Previous heart transplantation
- History of unstable angina, myocardial infarction, stroke, cardiovascular revascularization or open abdominal surgery within 6 weeks prior to the planned baseline visit
- Known pregnancy
- Patients on haemodialysis at baseline
- Unable to understand and comply with protocol or to give informed consent

NT-proBNP N-terminal pro-B-type natriuretic peptide

by biopsy in selected patients. These samples will be used for ex vivo and in vitro studies that are also described below. About 50% of patients with heart failure are women, but they are generally underrepresented in studies of heart failure, mainly because patients with left ventricular ejection fraction (LVEF) $>40\%$ have been excluded. Epidemiologically, about 70% of patients with LVEF $<40\%$ are men but 60% of patients with LVEF $>40\%$ are women. SICA-HF will recruit patients with a broad spectrum of LVEF, and therefore, we expect about half of all patients should be women, consistent with the known epidemiology [29].

2.3.1 Body composition analysis

In order to understand body composition and its changes over time in patients with CHF, SICA-HF will utilise two principal approaches to body composition analysis: first, body impedance assessment (BIA), and second, dual energy X-ray absorptiometry (DEXA) scanning. BIA is easily applicable to large patient cohorts using inexpensive equipment, and it provides information on the whole body; hence, it will be possible to use this technology in all

recruited patients. DEXA scanning is a more precise method that requires the use of significantly more expensive equipment that can provide body composition results for the whole body as well as any region of interest.

2.3.2 Peripheral blood flow

Peripheral blood flow and vascular reactivity will be assessed in the setting of CHF and the association specifically to insulin sensitivity and metabolic and hormonal regulation. Using venous occlusion (strain gauge) plethysmography, we will measure peripheral blood flow of the leg and of the forearm at rest, as post-ischemic peak blood flow and as flow-dependent flow.

2.3.3 Exercise testing and cardiopulmonary reflex research

Patients who are able, will undergo exercise testing, in most cases, using spirometry. In addition to standard parameters (peak oxygen consumption, ventilatory efficiency), we are planning to analyse numerous other parameters, including an integrative response in ventilation, oxygen consumption and carbon dioxide production, and heart rate during exercise and during recovery. Additionally, patients will undergo a comprehensive assessment of cardiopulmonary reflex control, including heart rate and blood pressure control, baroreflex, chemoreflex and ergoreflex sensitivity.

2.3.4 Insulin resistance

Non-diabetic subjects are scheduled to undergo whole-body insulin sensitivity testing using a 3-h intravenous glucose tolerance test and minimal modelling technique. Patients will be studied under standardised conditions (start in the morning, fasting, supine position, quiet room). After administration of a weight-adjusted glucose bolus intravenously, repeated serum samples will be obtained for profiles of glucose, insulin and C-peptide. From these profiles, individual insulin sensitivity can be assessed using the minimal modelling approach [30]. Assessment of the homeostasis model assessment, a reflection of insulin sensitivity and fasting plasma glucose will additionally be performed in a larger cohort of >500 subjects who have been prospectively recruited at the University of Hull after referral for suspected left ventricular dysfunction.

2.3.5 Sleep-disordered breathing

Two types of sleep-disordered breathing are common among patients with heart failure—obstructive sleep apnea–hypopnea (OSAH) and Cheyne–Stokes breathing (CSB). Risk factors for sleep-disordered breathing in patients with CHF vary according to the type of sleep-disordered

breathing. With respect to CSB, risk factors include male gender, advanced age, atrial fibrillation and hypocapnia (i.e. transcutaneous carbon dioxide ≤ 38 mmHg) [31]. With respect to OSAH, risk factors include advanced age and increasing BMI. Sleep-disordered breathing is best conceptualized as a sequence of events. In an effort to correct the hypocapnia, a hypersensitive respiratory control center initiates apnea. This occurs when the PaCO_2 is below the “apneic threshold”. The PaCO_2 then begins to rise. The duration from the beginning of the apnea until the respiratory control centre detects the increasing PaCO_2 is prolonged due to the increased circulatory time caused by the heart failure. Participating patients will be screened for sleep-disordered breathing using a standardised questionnaire, an ambulatory sleep–apnoea screening device and a 24-h ECG monitoring recorder with the measurement of peripheral oxygen saturation.

2.3.6 Blood and deoxyribonucleic acid bank

Subjects enrolled into SICA-HF will have blood samples taken to analyse biomarkers and gene profile in order to identify tools for diagnostic, prognostic and therapeutic guidance.

2.4 Investigations of metabolic and cellular mechanisms

SICA-HF aims to elucidate pathways that mediate tissue wasting and obesity in CHF by studying the interplay between muscle and adipose tissue wasting in cardiac cachexia and the role of skeletal muscle, an important factor for insulin resistance, in type 2 diabetes mellitus.

Adipose tissue samples will be obtained by liposuction in a subgroup of patients in SICA-HF and will serve as a basis for understanding the interplay between blood and tissue markers. Two potential mechanisms mediate loss of adipose tissue in cachexia: increased lipolysis or reduced lipogenesis [28]. Fat cells are sensitive to the lipolytic effects of atrial and B-type natriuretic peptides, both of which are found at elevated plasma concentrations in CHF [32]. Insulin is a key anti-lipolytic agent.

Skeletal muscle biopsies will be obtained in a subgroup of SICA-HF subjects using the Bergström needle technique. In cachexia, skeletal muscle is lost mainly by proteolysis, which is mediated by different mechanisms, including lysosomal (cathepsins) and calcium-dependent (calpains) pathways, the caspase system, matrix metalloproteinases and the adenosine triphosphate-dependent ubiquitin–proteasome system [25]. The latter plays a dominant role in myofibrillar protein breakdown [28]; however, data on patients with CHF are scarce.

Another important task of SICA-HF is to study the roles of circulating progenitor cells in patients with CHF in terms of their blood concentration, relationship to the clinical

severity of the disease, measures of heart function, and clinical outcomes. SICA-HF will investigate associations between circulating progenitor cells (as a reflection of the degree of endothelial dysfunction) and circulating angiogenic or anti-angiogenic growth factors and pro-inflammatory cytokines. Most of these substances have been shown to mobilise EPCs from the bone marrow.

Subjects participating in SICA-HF are scheduled for follow-up visits after 6–8 months and annually thereafter until the study terminates. The total duration of SICA-HF is 48 months. In accordance with local availability, not all the above tests can be performed in all participating centres.

2.5 Objectives

Using the above-described techniques, SICA-HF (<http://www.sica-hf.com>) is designed to evaluate the following primary objectives:

Objective 1: To characterise the prevalence, incidence, persistence and phenotype of obesity, cachexia and type 2 diabetes in patients with CHF

Objective 2: To describe patterns of exercise capacity and cardiorespiratory reflex control

Objective 3: To analyse body composition and its changes over time in patients with CHF and type 2 diabetes, obesity or cachexia

Objective 4: To investigate the incidence and prevalence of sleep-disordered breathing and its impact on the clinical severity in patients with CHF

Objective 5: To establish the impact of impaired vascular reactivity on impaired skeletal muscle metabolic and functional capacity, including its underlying mechanisms

Objective 6: To describe the interplay and metabolic signalling pathways between adipose tissue, skeletal muscle, the bone marrow and the heart in patients with heart failure and type 2 diabetes, obesity and cachexia

3 Discussion

SICA-HF is the first large-scale multicenter project to systematically collect information about the natural history of CHF and its interplay with three important and common co-morbidities: type 2 diabetes mellitus, cachexia and obesity. Importantly, SICA-HF embraces clinical and basic science research methodologies. One of the principle ideas of SICA-HF is that basic researchers will be provided with biomaterials such as adipose tissue and skeletal muscle biopsies from patients who have undergone a detailed, systematic set of clinical investigations. This will provide a wealth of information helping to understand cellular and

molecular mechanisms and to extend this knowledge into translation to clinical parameters.

Another important consideration in designing SICA-HF was to enrol patients irrespective of their LVEF. This is important because patients with preserved LVEF have received little scientific attention so far. Epidemiological and clinical characterisation, as well as therapeutic management, are much better established for patients with left ventricular systolic dysfunction. We do not know whether available evidence can be extrapolated to patients with preserved left ventricular ejection fraction [33]. Clustering of features of the metabolic syndrome, especially arterial hypertension may be particularly common in such patients. A recent study in 1,236 patients with heart failure and preserved ejection fraction, 44% of whom had a BMI >30 kg/m² found an increasing prevalence of arterial hypertension and diabetes mellitus across groups with increasing BMI [34]. Low BMI was associated with poorest survival, similar to previous observations in patients with left ventricular systolic dysfunction. Morbid obesity (BMI >45 kg/m²), however, also represented an increased risk, and a U-shaped relationship between BMI and mortality was described. Secondary analysis of the Digitalis Investigation Group ancillary trial (988 patients with LVEF >45%) focused on diabetes mellitus and reported a prevalence of 29% among patients with preserved LVEF [35]. Diabetics were more likely to be women, to have a history of hypertension and a higher BMI. Adverse CHF-related outcomes, including cardiovascular mortality and hospitalizations, were more common in diabetics. In an adjusted model, diabetes was associated with a 68% increased risk of hospitalisation for heart failure or heart failure-associated death [hazard ratio (HR) 1.68; 95% confidence interval (CI), 1.26–2.25].

Information about cachexia in CHF with preserved left ventricular ejection fraction is, to the best of the authors' knowledge, lacking, as well is information about body composition and a potential interplay with clinically detectable metabolic changes. Clustering of metabolic issues is known as the metabolic syndrome, which is associated with an increased risk for cardiovascular complications, including the incidence of heart failure [36]. In the general population, aggressive management is warranted whereas no guidance has been published for patients with CHF. Conversely, physicians are inclined to extrapolate knowledge from the general population or from patients with coronary artery disease without heart failure to patients who already suffer from overt heart failure. Available data about the metabolic syndrome in CHF is scarce and with certain methodological drawbacks. A retrospective study in 886 patients [37] used the National Cholesterol Education Program Expert Panel criteria with a BMI ≥30 kg/m² substituted for increased waist circumference

to confirm the presence of the metabolic syndrome in 625 (71%) patients. In a fully adjusted model, presence of the metabolic syndrome conferred, in contrast to the general population but in line with reverse epidemiology, a protective mortality effect (HR, 0.73; 95% CI, 0.56–0.94). It is evident that CHF has a clinically important metabolic component, but the applicability of the current metabolic syndrome definition [38] to patients with CHF has been challenged [39]. SICA-HF has the potential for in-depth investigations of metabolic issues and associated mechanisms to evaluate their effect on pathophysiology and outcome. The prospective design will allow to control for changes over time and to assess the implications for clinical presentation of CHF.

CHF is associated with activation of several mechanisms and body systems. Neurohormonal activation initially has protective effects but prolonged (over-) activity translates into clinically apparent damage mediated through neurohormonal and other mechanisms. This seems to be particularly important in the setting of cachexia, when highest concentrations of natriuretic peptides and markers of inflammation are detected [40]. Our knowledge about the activation and the interplay of existing systems [27, 41] and the level of induction remains insufficient, particularly so among patients with preserved left ventricular ejection fraction. Nonetheless, different organs are no longer considered as separated entities with specific and limited functions but rather as a well-controlled and interactive system. Even fat tissue, which was considered merely as an energy depot, emerges as a sophisticated endocrine organ with precisely adjusted function and effects beyond fat tissue itself [42]. Adiponectin, for instance, a collagen-like plasma protein produced by adipose tissue, which has in general anti-atherogenic and anti-inflammatory effects, is elevated in patients with CHF [43], which seems to be mediated through natriuretic peptides [44]. Data from preclinical experiments suggest that hypoadiponectinemia in hypertension-induced diastolic heart failure exacerbates left ventricular hypertrophy, diastolic dysfunction and diastolic heart failure [45]. Whether this has applications in patients and whether adiponectin replacement could be a novel therapeutic approach to prevent the progression to diastolic heart failure warrants further study.

SICA-HF will be the first detailed, systematic, longitudinal, international, epidemiological study of CHF, providing insights into the progression of cardiovascular and metabolic dysfunction and their relationship to outcome in patients with CHF. Thus, SICA-HF is a unique living laboratory that will help redefine CHF as a clinical entity and improve treatment of both cardiovascular and metabolic components of the disease in the next few decades.

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