Ph.D. thesis

Glucose Metabolism in Chronic Systolic Heart Failure
Relation to Left Ventricular Function, Exercise Capacity, and Mortality

Michael Egstrup
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The Faculty of Health Sciences, Copenhagen University, Denmark has approved this PhD dissertation for public defense. The public lecture and defense will take place Sep 14th, 2012 at 15.00 in the main Auditorium, Hovedvejen entrance 14, Frederiksberg University Hospital, Nordre Fasanvej 59, 2000 Frederiksberg.
In late 2007 my dawning scientific career was off to a bad start. A multicenter study was planned, but had to be abandoned for various reasons. With the prospect of being a Research Fellow without a research project, things looked somewhat grim. However, to the rescue came the visionary Professor Kenneth Egstrup and outlined a project which was not only feasible, but also based on echocardiography - my favorite cardiology tool. However, due to familial relations and geographic distances, I needed another senior MD to spearhead the project.

I approached Dr. Christian Tuxen who agreed to become my main academic advisor. Although slightly reluctant at first -this was his first time as a PhD advisor- once the decision was made Christian has been invaluable and certainly proved a responsible leader of such a project. I owe to him a great debt of gratitude not only for always making things possible, but also for his informal and empathic nature. Whenever problems arose, whether scientific or economic, logistic or technical, professional or personal, Christian’s door was always open for help and support.

I would like to direct a very special thank you to Dr. Ida Gustafsson who has been dedicated to this project far beyond what any PhD student could expect from an advisor. Ida invested so much time and effort in all aspects of the work leading to this thesis, that I often forgot that it was not actually her full-time occupation. Ida’s efforts are perhaps best described as “scientific perfectionism” in the best sense of the word, she has been exceptionally thorough, systematic, and eager to master any field of research related to the project. This has come to my benefit many times. I believe that Ida has been a guarantee for the optimal interpretation and presentation of my data whether in oral presentations or scientific papers. I am looking forward to her superb guidance in future research collaborations.

I have furthermore had the luck to be supervised by another two excellent clinicians and researchers. Dr. Caroline Kistorp has contributed with great insight into the interrelations between diabetes and heart failure, and she has been indispensable in the designing of the entire project. As an endocrinologist, Caroline has also provided the group’s diabetological expertise. The inclusion of Dr. Jacob Müller to the group of advisors indeed was a breakthrough for the project. Jacob excels in echocardiography and hemodynamics, which are core subjects of the project, and he is also an outstanding scientific author. Jacob has been a patient tutor in all of these areas, and without him the invasive sub-study of the project could not have been realized.

I have also had the privilege of working closely with Dr. Morten Schou. Although not formally a part of the advisor group, he has contributed generously with his tremendous awareness of the frontiers and trends of the scientific community and with vast knowledge of the scientific literature and -methodology. Although Morten has many innovative ideas, he is also a skeptic who enjoys challenging the project fundamentals – and to make you think it all through once again.

Dr. Per Hildebrandt deserves special mentioning for introducing me to the scientific environment connected to the heart failure clinics in the Copenhagen area. Per was vital for the assembly of the advisor group and for the initiation of the project.

Also thanks to Dr. Dan Høfsten for his help with the echocardiographic study protocol, Dr. Peter Jacobsen for his echocardiography tuition, Dr. Finn Gustafsson for excellent advice during manuscript writing, data extraction from “Hjerterplus”, and for his much-appreciated help with the invasive sub-study, and Dr. Mads Andersen for right heart catheterizations.

I am grateful towards the skilled nurses at the heart failure clinic, Frederiksberg Hospital, Anna Marie Jensen, Birgitte Carlsen, Christina Havniernikova, Gitte Leth, Hanne Bartholdy, and Susanne Groth who have assisted me with patient inclusion and many practicalities related to the project. Similarly, I have very much enjoyed the high spirits and friendliness of nurses Anita Meier and Dorte Raae at the Project Unit, dept. of Cardiology and Endocrinology, Frederiksberg Hospital.

I also wish to thank René Frederiksen, ViCare Medical A/S, for providing software solutions for the echocardiographic analyses, and Dr. Kaj Vinter and the department of clinical biochemistry, Frederiksberg Hospital, for conducting OGTT’s.

The following institutions deserve recognition for providing the financial support necessary for project completion: The Danish Heart Foundation (Hjerterforeningen), the Faculty of Health Sciences, University of Copenhagen, and the dept. of Cardiology and Endocrinology, Frederiksberg University Hospital.

Last but not least, I would like to thank my family, in particular my daughter Sofia for reminding me that playing is just as important as science, and my spouse Stine for her support and patience.

Michael Egstrup
February 2012
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List of Papers

This thesis was based on the following papers:


II. Egstrup M, Kistorp CN, Schou M, Høfsten DE, Møller JE, Tuxen CD, Gustafsson I. Abnormal glucose metabolism is associated with reduced left ventricular contractile reserve and exercise intolerance in patients with chronic heart failure. Eur Heart J Cardiovasc Imaging 2012; doi: 0.1093/ehjci/jes165


Abbreviations

2hPG  2-hour plasma glucose
ACE-I  Angiotensin converting enzyme inhibitor
ARB  Angiotensin receptor blocker
CI  Confidence interval
CV  Coefficient of variation
CVD  Cardiovascular disease
DM  Type-2 diabetes mellitus
E  Peak left ventricular early diastolic flow velocity
e’  Peak left ventricular early diastolic tissue velocity
FPG  Fasting plasma glucose
HbA1c  Glycated hemoglobin-A1C
IFG  Impaired fasting glucose
IGT  Impaired glucose tolerance
IHD  Ischemic heart disease
LA  Left atrial
LDDE  Low-dose dobutamine echocardiography
LV  Left ventricular
LVEF  Left ventricular ejection fraction
NT-proBNP  N-terminal pro-B-type natriuretic peptide
OGTT  Oral glucose tolerance test
s’  Peak left ventricular systolic tissue velocity
TDI  Tissue Doppler imaging
WHO  World Health Organization
1. Introduction

An adverse relationship between Type-2 diabetes mellitus (DM) and heart failure incidence, symptom severity, quality of life, risk of hospitalization, and mortality has been firmly established in epidemiological studies, but the pathophysiologic nature of this relationship is incompletely understood.

In the last decade, focus on glucose metabolism from a cardiologist’s perspective has been extended from frank DM only to the inclusion of lesser degrees of abnormal glucose metabolism, since the cardiovascular risk associated with hyperglycemia and insulin resistance may not be encompassed by the diagnostic criteria for DM.

We hypothesized that in patients with chronic systolic heart failure abnormal glucose metabolism is common and associated with increased left ventricular dysfunction, exercise intolerance, and mortality.

1.1 objectives

In outpatients with chronic systolic heart failure

1. To assess the prevalence of unrecognized diabetes and impaired glucose tolerance by oral glucose tolerance testing (Paper I).

2. To assess the impact of abnormal glucose metabolism on mortality (Paper I).

3. To investigate the association between glucose metabolism and left ventricular function (Paper II).

4. To investigate the association between glucose metabolism and exercise capacity (Paper II).

5. To evaluate the effects of treatment in an outpatient heart failure clinic on disease severity and left ventricular function in relation to glucose metabolism (Paper III).

6. To investigate the hemodynamic response determined by right heart catheterization and the correlations with LV systolic function, diastolic function, and filling pressure during low-dose dobutamine echocardiography (Paper IV).

1.2 Background

1.2.1 Glucose metabolism and the risk of incident heart failure

Type-2 DM is characterized by increased plasma glucose concentrations due to resistance of insulin actions in the liver and peripheral tissues. Frank DM is preceded by several years of insulin resistance which is initially compensated for by increased insulin production. With time, insulin resistance increases while insulin production plateaus and finally decreases due to beta cell exhaustion. This is reflected by a gradual rise in postprandial glucose concentration and with further deterioration of homeostasis by a concomitant rise of fasting glucose concentration (Figure 1).

Specific plasma glucose thresholds have been defined for the diagnosis of DM and for the pre-diabetic glucose abnormalities impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). These thresholds are based on evidence of a steep increase in the risk of microvascular disease and of progression to frank DM respectively. The risk of developing cardiovascular disease, however, has been shown to increase with rising plasma glucose concentrations even below the thresholds of IFG/IGT.

Nevertheless, classification based on fasting- and standardized postprandial glucose concentrations during an oral glucose tolerance test (OGTT) has proved to be a clinically useful tool for cardiovascular risk stratification. Several large population studies have shown an association between abnormal glucose metabolism and the risk of developing heart failure. In the Framingham Study, the risk of incident heart failure was two-fold higher in men and five-fold higher in women with DM. In the Reykjavik Study, the age-adjusted odds ratios for incident heart failure were 2.7 in DM patients and 1.7 in IGT/IFG patients compared with normal glucose tolerance patients. The Atherosclerosis Risk In Communities Study showed an association of mean glucose concentrations evaluated by glycated hemoglobin (HbA1c) and the risk of incident heart failure in persons without DM and other studies have demonstrated similar findings for fasting plasma glucose (FPG) and the risk of incident heart failure in persons without DM and other studies have demonstrated similar findings for fasting plasma glucose (FPG). Despite the well-known association of DM with atherosclerosis, the risk associated with DM is not limited to ischemic heart failure. The odds ratio for the presence of DM in patients with a first diagnosis of non-ischemic dilated cardiomyopathy has been estimated to be 1.75.

1.2.2 Prevalence and prognostic implication of abnormal glucose metabolism in chronic heart failure

Given the increased risk of new-onset heart failure in patients with DM as well as less severe glucose abnormalities, the prevalence of these conditions in heart failure populations would be expected to be higher than predicted from that of the background population. In European outpatient systolic heart failure
1.2.4 Glucose metabolism and left ventricular function

An increased risk of developing heart failure independently of IHD and hypertension and the poor outcome in diabetic heart failure patients has led to the suggestion of a "diabetic cardiomyopathy". Compromised longitudinal LV diastolic and systolic contraction reserve have been shown in diabetic patients even in the absence of hypertension, left ventricular hypertrophy and IHD, and DM confers an additive effect on LV functional reserve impairment in patients with hypertension. Furthermore, abnormal glucose has been associated with diastolic dysfunction in otherwise healthy individuals and in patients with risk factors for heart failure. These associations may even exist in what is considered the normal glycemic range, which suggests an impact of abnormal glucose metabolism on LV function years before frank DM is diagnosed.

After an acute myocardial infarction, DM is an independent predictor of the development of heart failure and has been associated with greater impairment of diastolic LV function despite an apparent similar extent of the initial myocardial insult. A recent study reported an association between pre-diabetic glucose abnormalities classified by OGTT and reduced systolic and early diastolic tissue velocities.

Studies investigating LV function in systolic heart failure patients with and without abnormal glucose metabolism are few. Apparently, there is no significant difference in the resting LVEF between patients with or without DM, but whether diastolic function or LV functional reserve could be impaired in heart failure patients with glucose abnormalities remains unknown.

1.2.6 Glucose metabolism and the effect of heart failure treatment

No prospective studies have examined the effect of pharmacological heart failure treatment on mortality, LV function, or exercise tolerance specifically in patients categorized by glycemic status. The existing evidence is thus primarily derived from post hoc analyses of subgroups with pre-existing DM in major clinical trials evaluating the efficacy of specific drug- or device therapies. In most of these trials the reduction in mortality and hospitalization rates in patients with and without DM is similar. Whether the use of evidence-based treatment differs in heart failure patients with and without abnormal glucose metabolism is unknown. Also, multidisciplinary intervention in a heart failure clinic is effective in reducing morbidity, but knowledge of the benefit in diabetic patients is lacking.
Figure 1: Natural history of type-2 diabetes

2. Hypotheses

Based on the current knowledge we hypothesized that in patients with chronic systolic heart failure

1. Screening for abnormal glucose metabolism with oral glucose tolerance testing detects a substantial proportion of patients with diabetes and impaired glucose tolerance.

2. Diabetes, known or newly diagnosed, is a predictor of increased all-cause mortality compared to patients without diabetes.

3. The severity of abnormal glucose metabolism is associated with exercise intolerance and with poorer left ventricular function assessed by echocardiographic estimates of left ventricular filling pressure and contractile reserve.

4. Abnormal glucose metabolism is associated with a reduced impact of structured intervention in a heart failure clinic on left ventricular function assessed by improvement in echocardiographic estimates of left ventricular ejection fraction and in NT-proBNP concentrations after 6 months.
3. Methods

3.1 Study design and populations
This thesis was based on 2 prospective single-center cohort studies. All patients were consecutively screened from a special-ized outpatient heart failure clinic. The studies were approved by the Danish Data Protection Agency and the regional Scientific Ethics Committee of the Capital Region.

3.1.1 Design of the heart failure clinic
The heart failure clinic is a nurse-guided, physician-supervised clinic located at Frederiksberg University Hospital and involved in the diagnosis and treatment of chronic systolic heart failure. The clinic serves a catchment area of approximately 130,000 inhabitants. A diagnostic unit evaluates referrals for suspected chronic systolic heart failure and patients are transferred to the therapeutic unit if this diagnosis is confirmed. Confirmation requires fulfillment of the ESC diagnostic criteria for chronic systolic heart failure and a documented LVEF ≤ 45% primarily evaluated by echocardiography. Further investigation of the etiology of heart failure is undertaken when indicated. Evidence-based pharmacological-, invasive- and device treatments are instituted according to national and international guidelines. The amount and frequency of visits are tailored to individual requirements, and patients are educated in disease management and self-care, including the self-adjustment of diuretic dose. Patients are furthermore offered assistance in smoking cessation and a physical rehabilitation program.

3.1.2 Study populations and participation criteria
Study I
A total of 413 patients with confirmed systolic heart failure were screened for participation in study I at the first visit at the heart failure clinic during the period from April 2005 to August 2009. 309 patients either completing an OGTT or with a prior diagnosis of DM were included (Figure 2).

Inclusion criteria:
1. Confirmed systolic heart failure and LVEF ≤ 45%
2. Acceptance of OGTT in patients without a prior diagnosis of DM

Exclusion criteria: None

Study II and III
Patients were recruited from May 2008 to July 2010 within 1 week from transferal to the therapeutic heart failure unit. 282 patients were screened for participation and 161 included (study II). After 6 months all surviving patients without major ischemic events were invited to a repetition of the baseline examinations and 136 accepted (study III).

Inclusion criteria:
1. Confirmed systolic heart failure and LVEF ≤ 45%
2. Written informed consent

Exclusion criteria:
1. Significant aortic or mitral valve disease
2. Permanently paced heart rhythm
3. Mental or language barriers preventing informed consent
4. Contraindications to dobutamine infusion

Study IV
Sixteen patients were recruited among subjects completing study II and III, and right heart catheterization was feasible in 14. In addition to the participation criteria for study II and II, fulfillment of the following criteria was required:

Inclusion criteria:
1. Stable patient on optimal medical heart failure therapy defined as:
   a. Recommended or maximal tolerated doses of ACE-inhibitor or angiotensin II receptor antagonist and
   b. Recommended or maximal tolerated dose of beta receptor antagonist and
2. No signs of fluid retention on physical examination
3. Sinus rhythm
4. Written informed consent

Exclusion criteria:
1. Poor echocardiographic acoustic window
2. Recent device implantation (< 3 months)

3.2 Study program and data storage
Patients enrolled in study I completed an OGTT and laboratory tests within two weeks from the first visit at the heart failure clinic. The study programs for studies II-IV are outlined in Figure 3.

Patients were considered to have ischemic heart disease if any of the following characteristics were present: Previous myocardial infarction, previous revascularization, significant coronary artery stenosis on a coronary angiogram, or findings of significant perfusion defects during myocardial perfusion imaging.

Clinical characteristics, laboratory test results, 6-minute walking distance, pulmonary function measurements, and quality of life scores were entered into a database (“HjerterPlus”) immediately after the completion of the tests.

3.3 Assessment of glucose metabolism
3.3.1 Oral glucose tolerance test
All patients without a diagnosis of DM prior to study entry completed a standardized OGTT within 2 weeks from the first visit at the heart failure clinic. After an overnight fast of at least 8 hours and 20 minutes of supine rest, blood samples were obtained from an antecubital vein and FPG was measured. Within 5
minutes from the fasting blood sample patients ingested a solution containing 75 g of glucose dissolved in 250 ml of water. Two-hour plasma glucose was measured from the plasma concentration of glucose in a blood sample drawn after a further 120 minutes of rest.

From the FPG and 2hPG patients were classified according to the WHO 1999 diagnostic criteria for plasma glucose measurements as having normal glucose tolerance, IGT or newly diagnosed DM (Table 1).

<table>
<thead>
<tr>
<th>Normal glucose metabolism</th>
<th>Abnormal glucose metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FPG (mmol/L)</strong></td>
<td><strong>IGT</strong></td>
</tr>
<tr>
<td>&lt; 6.1</td>
<td>≥ 6.1 and &lt; 7.0</td>
</tr>
<tr>
<td>2hPG (mmol/L)</td>
<td>&lt; 7.8</td>
</tr>
</tbody>
</table>

### 3.3.2 Glycated hemoglobin
From the fasting blood samples collected at baseline and follow-up visits, HbA1c was measured with an immuno-turbidimetric assay, using alkaline hematin D-575, on a Cobas Integra analyzer (Roche Diagnostics, Basel, Switzerland).

### 3.3.3 Insulin resistance
Insulin resistance was indirectly assessed from FPG and fasting insulin concentrations using the homeostatic model assessment (HOMA-IR)\(^76\) formula (FPG x fasting insulin / 22.4) in patients in study II and III.

### 3.4 Assessment of left ventricular function by echocardiography

#### 3.4.1 Study II and III
Echocardiography was conducted by a single investigator and performed on a Philips IE-33 cardiac ultrasound system with an SS-1 trans-thoracic transducer (Philips Healthcare, Andover, Massachusetts, USA). Images were stored digitally and assigned an encrypted identification code. Analyses were conducted on an offline software analysis system (Philips Xcelera) after the completion of echocardiography in all patients.

Echocardiography was conducted 1 week from study enrollment (study II) and repeated after 6 months of follow-up (study III) by the same investigator. All examinations were performed according to a predefined protocol with comprehensive image acquisitions at rest and immediately afterwards repeated during infusion of dobutamine. For Doppler and TDI measurements of at least five consecutive beats were analyzed in patients in sinus rhythm and 10 beats in patients in atrial fibrillation while disregarding ectopic and post-ectopic beats.

The following measurements of LV structure and function were measured during rest and LDDE with the exception of LV outflow tract diameter and left atrial volume measurements, which were only obtained at rest.

#### 2-dimensional measurements and calculations
The diameter of the LV outflow tract, internal LV diameter and wall-thickness during end-diastole and end-systole were obtained from the parasternal long-axis view. LV mass was calculated by a validated formula\(^77\). From the apical 4- and 2-chamber views the LV endocardial border was traced at end-diastole and –systole and LVEF, diastolic and systolic volumes calculated by the modified biplane method of discs\(^77\). Left atrial (LA) volume was similarly calculated from tracings of the end-systolic frame prior to mitral valve opening in 4- and 2-chamber apical projections adjusted to maximize LA area. LA volume index was calculated by the division of LA-volume with body surface area.

#### Doppler measurements and calculations
The trans-mitral flow profile was obtained from the apical 4-chamber projection using the pulsed-wave Doppler technique. A 2 mm sample volume was placed at the tips of the mitral leaflets during diastole after color aided alignment of the Doppler beam to flow direction and images recorded at a horizontal sweep speed of 100 mm/s. Maximal early (E-wave) and late (A-wave) diastolic trans-mitral flow velocities and deceleration time of the E-wave were measured and the E/A-ratio calculated.

Pulsed-wave Doppler of the LV outflow tract was similarly recorded from either apical 5-chamber or long-axis view the choice of which depended on the best alignment of the Doppler beam with flow direction. The stroke distance was measured by tracing of the flow profile and cardiac output calculated by multiplying stroke distance with LV outflow tract area and heart rate at the time of image acquisition.

The time from the QRS complex to the end of systolic aortic flow assessed by pulsed wave Doppler of the LV outflow tract (apical 5-chamber view) and to the beginning of mitral inflow assessed by pulsed-wave tissue Doppler of mitral inflow (apical 4-chamber view) were measured. The isovolumetric relaxation time was calculated as the difference between these time intervals.

#### Tissue Doppler measurements and calculations
Measurements of maximal longitudinal systolic (s'), early (e') and late (a') diastolic myocardial tissue velocities were obtained from 6 corners of the mitral annulus using pulsed-wave TDI in the apical 4-chamber, 2-chamber, and long-axis views. A 2 mm sample volume was placed in the ventricular wall just adjacent to leaflet insertion points during systole. An average of the velocities was calculated and considered a measure of global LV longitudinal tissue velocity. The ratio of maximal early diastolic flow velocity to maximal global early diastolic tissue velocity (E/e') was calculated.

#### Low-dose dobutamine echocardiography
Immediately after completion of the resting echocardiogram infusion of intravenous dobutamine was administered at a rate of 5 µg/kg/min. After 3 minutes the infusion rate was increased to 10 µg/kg/min, which was the target dose. After 3 minutes LDDE images were acquired during continuous dobutamine infusion. Blood pressure was measured prior to dobutamine infusion and after dose increments. Heart rate and rhythm was monitored for the duration of the examination. The examination was terminates prematurely in case of patient discomfort or adverse reac-
7.5 F triple-lumen Swan-Ganz thermistor and balloon-tipped Right heart catheterization was performed by introducing a right heart catheterization and echocardiography. Invasive displayed in Table 2, and the corresponding Bland-Altman as well as calculation of the coefficient of variation. The results are reported as mean difference with 95% levels of agreement as with a beta-blocker was not discontinued in relation to LDDE.

3.4.2 Study IV
Echocardiography in study IV was performed using the same image acquisition protocol as in study II and III, but with the addition of a second LDDE-stage with an infusion rate of 20 µg/kg/min. Similarly, dobutamine was infused at this rate for 3 minutes before image acquisition and continued until the examination was completed.

3.5 Reproducibility of primary echocardiographic parameters
Inter- and intra-observer variability was determined by repeated analysis of 20 echocardiographic examinations by the primary investigator and an experienced cardiologist. The variability is reported as mean difference with 95% levels of agreement as well as calculation of the coefficient of variation. The results are displayed in Table 2, and the corresponding Bland-Altman concordance plots in Figure 4.

<table>
<thead>
<tr>
<th></th>
<th>Intra-observer variability</th>
<th>Inter-observer variability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean difference (95% level of agreement)</td>
<td>Mean difference (95% level of agreement)</td>
</tr>
<tr>
<td>Rest E (cm/s)</td>
<td>-0.1 (-6.4-6.1)</td>
<td>4.2%</td>
</tr>
<tr>
<td>Rest e'(cm/s)</td>
<td>-0.02 (-0.6-0.5)</td>
<td>4.6%</td>
</tr>
<tr>
<td>Rest E/e'</td>
<td>0.03 (-1.9-1.9)</td>
<td>7.3%</td>
</tr>
<tr>
<td>Rest s'/cm/s</td>
<td>0.02 (-0.4-0.4)</td>
<td>3.7%</td>
</tr>
<tr>
<td>Rest LVEF (%)</td>
<td>2.8 (-9.4-15.0)</td>
<td>16.2%</td>
</tr>
<tr>
<td>LDDE E (cm/s)</td>
<td>-0.9 (-11.9-10.1)</td>
<td>6.7%</td>
</tr>
<tr>
<td>LDDE e'(cm/s)</td>
<td>-0.2 (-1.1-0.6)</td>
<td>5.9%</td>
</tr>
<tr>
<td>LDDE E/e'</td>
<td>0.3 (-2.1-2.7)</td>
<td>10.3%</td>
</tr>
<tr>
<td>LDDE s'/cm/s</td>
<td>0.2 (-0.9-1.4)</td>
<td>7.6%</td>
</tr>
<tr>
<td>LDDE LVEF (%)</td>
<td>3.1 (-10.7-16.8)</td>
<td>14.7%</td>
</tr>
</tbody>
</table>

3.6 Invasive measurements of hemodynamic parameters
Patients enrolled in study IV were evaluated with simultaneous right heart catheterization and echocardiography. Invasive measurements conducted at rest were repeated at the 10 and 20 µg/kg/min LDDE stages.

Right heart catheterization was performed by introducing a 7.5 F triple-lumen Swan-Ganz thermistor and balloon-tipped catheter to the right internal jugular vein and advancing through the right atrium and ventricle to a proximal pulmonary artery into an optimal position for the measurement of the pulmonary capillary wedge pressure (PCWP), which is an estimate of LV filling pressure. PCWP was obtained by briefly inflating the balloon at rest and during the 2 LDDE stages. Cardiac output was determined at rest and LDDE stages by the principle of thermodilution using an average of three measurements. Central venous pressure and pulmonary artery systolic and diastolic pressures were measured at rest and during LDDE stages.

3.7 Assessment of exercise tolerance
A standardized 6-minute walking distance test (6MWD) was conducted after the echocardiographic examinations in study II and III. The test was conducted in an indoor hallway at laps of 30 meters. Patients were instructed to walk as far as possible during the 6 minutes and motivated to keep the pace according to recommendations. The distance covered was then noted. Patients with significant physical disabilities were excluded.

3.8 Laboratory tests
Fasting blood samples were drawn at the time of OGTT (study I and II), prior to follow-up visits (study III) and prior to study IV and was, in addition to FPG, HbA1c and fasting insulin concentrations, analyzed for creatinine, hemoglobin, cholesterol, and NT-proBNP.

3.9 Treatment during follow-up
Treatment during follow-up was decided by the attending physicians. Daily dosages of ACE-inhibitors (ACE-I), angiotensin receptor blockers (ARB), beta-blockers, and loop-diuretics as well as treatment with digoxin and aldosterone antagonists was recorded at baseline and follow-up.

3.10 Outcomes
Survival status among patients participating in study I was obtained from the Danish Civil Personal Registry on September 1st 2009 yielding a median follow-up time of 19.4 months (interquartile range 10.3-33.8 months).

The chosen primary outcome measures in study III were an increase in LVEF of at least 5% and a decrease in NT-proBNP of at least 30%.

3.11 Statistics
Statistical analyses were conducted by the principal investigator aided by a statistics consultant and co-authors. SPSS statistics 20 (IBM corp.) was used for all analyses. Specific analyses used in studies I-IV are described in detail in the respective papers.

In general, continuous data are presented as means (SD) and differences between glycemic groups evaluated by one-way ANOVA. A least significant difference test was used post-hoc to compare individual abnormal groups with normal glucose tolerance patients. Within-group changes were compared using a paired T-test. Proportions are presented as a count (%), between-group differences compared using a $\chi^2$ test, and within-group changes using McNemar’s test. For continuous variables with a non-normal distribution, data is presented as median (interquartile range), between group differences compared using the Kruskal-Wallis equality of populations rank test, and within-group changes using a related-samples Wilcoxon Signed Rank test. A two-sided P-value < 0.05 was considered statistically significant.

To ensure the appropriateness of covariates included in linear regression models, residuals plots were produced and inspected visually. The assumption of proportional hazards for covariates included in Cox regression models were tested by
inspection of log-log plots. The number of covariates included in multiple regression models was limited according to the number of patients or events. In addition to age and gender, the covariates judged most clinically relevant were included in the models. Patients with missing parameter values in any covariate were excluded from analyses.

3.11.1 Sample size calculation

The sample size calculation for study II was based on differences in $E/e'$ during LDDE in acute myocardial infarction patients with and without DM. Data was obtained from a retrospective review of a recently completed study (Department of Medical Research, Funen Hospital Svendborg). We abandoned this parameter prior to data analysis due to the lack of correlation with invasively estimated LV filling pressure during LDDE.

In that study 61 patients had a LVEF $\leq$ 45%. Mean $E/e'$ during LDDE was 11.8 (SD 4.6). In patients with known or newly detected diabetes (40% of the cohort) mean $E/e'$ during LDDE was 40% higher in DM patients than patients without DM (14.3 vs. 10.2). Based on these results, we designed our study to detect an elevation of $E/e'$ of 25% or more in DM patients compared to patients without DM (13.4 vs. 10.7 if assuming a mean of 11.8) which was considered clinically relevant. If assuming a similar prevalence of diabetes as well as standard deviations of $E/e'$ as in this retrospective study, at least 130 patients should be included (52 of whom are expected to have known or newly detected DM) for the study to have a power of 0.9 to detect such a difference at a two sided alpha level of 0.05.
Figure 2: Study flow charts

Figure 3: Study program. Study II, III, IV

First visit at the heart failure clinic
- Referral to primary investigator

Study enrollment (< 1 week)
- Clinical data collection and evaluation of IHD status

Study II examinations (< 2 weeks)
- OGGT and laboratory tests
- Low-dose dobutamine echocardiography
- 6-minute walk test
- Pulmonary function test
- Quality of life assessment

Study III examinations (6 months)
- Laboratory tests
- Low-dose dobutamine echocardiography
- 6-minute walk test
- Pulmonary function test
- Quality of life assessment

Study IV examinations
- Simultaneous right heart catheterization and low-dose dobutamine echocardiography
Figure 4a: Bland-Altman concordance plots of intra- and inter-observer variability of resting echocardiography.
Figure 4b: Bland-Altman concordance plots of intra- and inter-observer variability of LDDE echocardiography
4. Summary of results

4.1 Paper I

Oral glucose tolerance testing in an outpatient heart failure clinic reveals a high proportion of undiagnosed diabetic patients with an adverse prognosis.

Of 413 consecutively screened patients 82 (20%) had a diagnosis of DM prior to study enrollment. Of 331 patients without known DM 227 (69%) accepted an OGTT, and of these 136 (60%) were classified as normal glucose tolerance, 51 (23%) as IGT, and 40 (18%) as newly diagnosed DM. Sixteen of 40 with newly diagnosed DM would have been undetected by FPG alone. During a median follow-up time of 591 days (interquartile range 314-1028) 89 (22%) patients died. The mortality rate was highest among unclassified patients and in patients with known DM, while it was lowest among patients with normal glucose tolerance. Intermediate mortality rates were observed in patients with IGT and in those with newly diagnosed DM (Figure 5). Diabetes, known or newly detected, was an independent predictor of all-cause mortality (hazard-ratio 1.91, 95% CI 1.02-3.59, P=0.044). This was not the case for IGT and newly diagnosed DM compared to normal glucose tolerance where hazard-ratios did not reach statistical significance.

Figure 5: Kaplan-Meier curves illustrating cumulated survival according to glycemic status (left) and diabetes (right)
4.2 Paper II

Abnormal glucose metabolism is associated with reduced left ventricular contractile reserve and exercise intolerance in patients with chronic heart failure

Of 268 screened patients 161 (60%) fulfilled inclusion criteria and were examined by low-dose dobutamine echocardiography (LDDE) and 6-minute walk test. Glucose metabolism was characterized by a known DM diagnosis (N = 34) or OGTT (N=127).

Compared to normal glucose tolerance, patients with known DM had significantly reduced resting LVEF (39.1±9.6% vs. 33.4±9.5%, P=0.006), s’ (5.8±1.3 cm/s vs. 5.3±1.6 cm/s, P=0.04), and elevated E/e’ (11.4±5.0 vs. 13.9±4.8, P=0.02). Newly diagnosed DM patients had elevated E/e’ (13.9±5.9, P=0.03), while IGT patients did not differ from normal glucose tolerance patients. Newly diagnosed and known DM were independently associated with a reduced LVEF reserve detected by dobutamine stimulation compared to normal glucose tolerance patients (-3.5%, P=0.035 and -5.4%, P=0.001, respectively) (Figure 6).

The 6MWD was found to be reduced with more severe abnormal glucose metabolism, but this was only significant for new and known DM compared to normal glucose tolerance when controlling for several potential clinical confounders. Further adjustments for LVEF during LDDE and E/e’ at rest did not alter these results (Figure 6). In addition, an independent inverse linear association was observed between 2-hour plasma glucose and 6MWD (Figure 7).

![Figure 6: Crude and adjusted estimates of LV contractile reserve and 6-minute walking distance according to glycemic classification](image)

![Figure 7: Relationship between 2-hour plasma glucose and 6-minute walking distance](image)
4.3 Paper III

Effects of treatment in an outpatient heart failure clinic on disease severity and left ventricular function in relation to glucose metabolism

Of 161 patients included at the first visit in a heart failure clinic 136 without any major ischemic events completed a follow-up visit after 6 months. At follow-up newly detected and known DM patients received lower mean doses of ACE-I/ARB than NGT patients (65±39% and 67±43% vs. 86±31% of recommended dosage). There were no significant differences between prescribed dosages of beta-blockers or the proportion of patients receiving aldosterone antagonists among the groups. Compared to patients without a prior DM diagnosis, known DM patients had similar chance for improvement in resting LVEF (odds ratio for ≥ 5% increase: 2.2, P=0.14), but significantly lower odds for improved LDDE LVEF (odds ratio for ≥ 5% increase: 0.1 (95% CI 0.02-0.6), P=0.001). In the patient group without known DM, increasing 2hPG concentration was not associated with increase in LVEF. Neither known DM nor 2hPG were independently associated with an NT-proBNP reduction ≥ 30% from baseline to follow-up (Figure 8).

**Figure 8: Adjusted odds ratios for improvement in LVEF and NT-proBNP according to known DM status or 2hPG**

![Diagram showing odds ratios for improvement in LVEF and NT-proBNP](image-url)
4.4 Paper IV

Hemodynamic response during low-dose dobutamine infusion in patients with chronic systolic heart failure: Comparison of echocardiographic and invasive measurements

Simultaneous echocardiographic and right heart catheterization measurements were performed at rest and during 2 stages of LDDE in 14 patients. Cardiac output increased significantly from rest (4.9±1.2 L/min) to LDDE stage 1 (+0.8±1.2 L/min, P=0.03) and stage 2 (+1.7±1.3 L/min, P<0.001) with only slight changes in blood pressure and systemic vascular resistance and unchanged heart rate. Mean PCWP (16.6±8.3 mmHg) was not significantly changed during LDDE but the response varied in individual patients. Doppler echocardiographic parameters reflecting early diastolic trans-mitral flow velocity (E), early diastolic lengthening velocity (e'), and systolic tissue velocity (s') all increased significantly during LDDE, whereas the E/e' ratio was unchanged. s' had a moderate correlation with cardiac output at rest (R=0.61, P=0.02) that became stronger during LDDE stage 1 (R=0.71, P=0.004) and stage 2 (R=0.79, P<0.001). The E/e' was correlated with PCWP at rest (R=0.64, P=0.014) but not during LDDE (Figure 9).

Figure 9: Correlation of E/e' with pulmonary capillary wedge pressure at rest during dobutamine infusion

![Figure 9](image-url)
5. Methodological considerations

5.1 Low-dose dobutamine echocardiography
Low-dose dobutamine echocardiography is a cheap and safe test in stable heart failure patients. Dobutamine is predominantly a β1-adrenergic agonist, with weak β2 activity, and α1 selective activity and augments contractility with subtle changes in heart rate and loading conditions at low doses, which makes it suitable for the evaluation of LV contractile reserve. The LV contractile reserve is a predictor of exercise capacity, response to beta-blocker therapy and CRT, and mortality in systolic heart failure patients. Furthermore, dobutamine stimulation has been used to identify reduced LV contractile and diastolic function in DM patients without detectable differences at rest. For these reasons we hypothesized that inotropic stimulation with dobutamine could reveal LV dysfunction with functional and prognostic relevance that would not be detected by resting echocardiography. Although LDDE does not offer the physiologic hemodynamics and physical capacity estimate of exercise echocardiography, we preferred LDDE because the image acquisition is easier and this method is more feasible in an elderly population with possible musculoskeletal co-morbidities.

It is however not known to which extent the echocardiographic parameters reflect the hemodynamic status during LDDE in systolic heart failure patients. We therefore compared invasive measures of LV filling pressure and cardiac output with Doppler measures of LV function during rest and LDDE (study IV). While the systolic lengthening velocity reflected contractile function more strongly during LDDE than at rest, the E/e’ ratio did not predict LV filling pressure during LDDE, which warrants caution in the interpretation of this parameter during dobutamine infusion. This has also recently been shown for patients without systolic dysfunction. As a consequence, we chose contractile reserve instead of diastolic reserve as the principle echocardiographic outcome measure during LDDE.

In study III we chose an increase in LVEF of 5% or more to represent a clinically meaningful improvement. A lower increase may also be beneficial, but the variation in repeated measurements of LVEF by the biplane method of discs did not allow detection of minor changes. We preferred this method for the quantification of LV systolic function over wall motion scoring, since a large proportion of patients did not have segmental dysfunction. A simple segmental score would not be able to detect relatively subtle global contractility increases in these patients.

Some patients have poor acoustic windows which impedes the production of clear echocardiographic images. This is problematic for an accurate endocardial tracing used for the calculation of LVEF by the biplane method. In the current studies, patients with too poor image quality to accurately trace the endocardium were excluded from analyses which included LVEF.

5.2 Oral glucose tolerance test
Heart failure is recognized as a state of insulin resistance. Thus, in addition to a possible direct contribution of insulin resistance and abnormal glucose metabolism to heart failure development, the degree of insulin resistance and hyperglycemia may also be influenced by and serve as a marker of heart failure severity (Figure 10).

A rise in postprandial glucose concentration in response to insulin resistance occurs prior to a rise in fasting glucose and overall glycemic burden assessed by HbA1c (Figure 1). Thus, elevated 2hPG is an early sign of abnormal glucose metabolism that remains undetected without an OGTT. Moreover, both insulin resistance and isolated postprandial hyperglycemia have been associated with impaired LV structure and function. Postprandial glucose concentrations may therefore carry information beyond FPG and HbA1c in heart failure patients as well. Also, at the time of designing this study OGTT screening of all patients with CVD was recommended although data supporting this practice in heart failure patients was lacking. For these reasons we chose to characterize the study population metabolically by applying OGTT in addition to fasting insulin and HbA1c.

5.3 6-Minute walking distance test
The cardiopulmonary exercise test (CPET) is the gold standard for the evaluation of exercise capacity, but it requires expensive equipment and the incremental work-load imposed may not be well-tolerated in heart failure patients. Conversely, the 6MWD is a cost effective, safe, and reproducible test, a reliable substitute for the CPET, and is associated with functional class and mortality in a variety of chronic heart failure populations. The 6MWD is well-tolerated in heart failure patients and may be better than peak exercise performance tests in patients on beta-blockers. Furthermore, the 6MWD has been found to be lower in diabetic heart failure patients. We therefore considered the 6MWD suitable for serial measures of exercise capacity as well as a possible marker of prognosis in relation to glucose metabolism in chronic heart failure patients.

5.4 NT-proBNP
NT-proBNP was chosen as a marker of heart failure severity and a measure of treatment response. A single measurement of NT-proBNP is known to carry important prognostic information and serial measurements in response to treatment have been shown to further enhance risk stratification in patients with heart failure. However, the long-term clinical variability of serial NT-proBNP measurements is considerable and changes must accordingly be carefully interpreted. We therefore chose a NT-proBNP reduction of 30% or more to represent a clinically meaningful reduction.
Figure 10: Promotion of insulin-resistance, hyperglycemia, and diabetes mellitus by the heart failure syndrome

6. Discussion

6.1 Prevalence and prognostic impact of abnormal glucose metabolism in chronic systolic heart failure

An OGTT is recommended as a screening tool in chronic heart failure patients, since the prevalence of unrecognized abnormal glucose metabolism is expected to be high and to be associated with risk. In patients with IHD such screening has repeatedly been reported to detect abnormal glucose metabolism in more than half of patients without known DM. Since IHD is the most common cause of chronic systolic heart failure the former recommendation appears reasonable. We found that in addition to a prevalence of known DM of 20%, more than 40% of the remaining population could be classified as IGT or newly diagnosed DM by OGTT. Only few small studies with information on the prevalence of abnormal glucose metabolism exist. The direct comparison between our studies and others is complicated by the heterogeneity of patient populations with respect to several factors: acute vs. chronic heart failure, hospitalized patients vs. outpatients, reduced vs. preserved LVEF, region of study conduct, and ischemic vs. non-ischemic etiology, but the findings of substantial proportions with IGT or newly diagnosed DM are undeviating in all studies (Table 3). The prevalences of known DM and OGTT-detected DM and IGT were substantially higher than those found in the general population.

While it is well known that frank DM is associated with increased risk in chronic heart failure patients almost doubling the mortality risk compared to patients without known DM, the implication of less severe glucose abnormalities is incompletely understood due to conflicting results in previous studies. This is likely explained by differences in study-specific definitions of abnormal glucose metabolism, and variations in population characteristics such as those described above.

With OGTT we were able to define DM not only by history or fasting glucose concentration, but also by postprandial glucose concentrations. Similarly, the absence of elevation of both fasting and postprandial glucose concentrations was a prerequisite for normal glucose tolerance status. We were thus able to compare patients with known DM to patients with completely normal glucose concentrations. In contrast, previous studies compared DM patients to patients with unknown glycaemic status, of whom a large proportion could be expected to be abnormal. This may explain that known DM in our study was independently associated with a 3-fold higher mortality risk than normal glucose tolerance patients, whereas in all DM patients (known and newly detected) the mortality was 1.9 times higher than in patients without DM. Although our study was underpowered to detect a significantly increased mortality among patients with either IGT or newly diagnosed DM, the crude analyses suggested these patients to be at intermediate risk similar to the observations among patients with coronary artery disease. These findings support the recommendation of an OGTT to improve risk-stratification in heart failure populations.

Since the time of designing this study HbA1c has been introduced for the diagnosis of DM. Additional analyses on our data revealed that HbA1c did not influence mortality when considered on a continuous scale or by using 6.5% as cut-off limit (data not shown).

6.2 Glucose metabolism and LV function in chronic systolic heart failure

The relationship between glucose metabolism and LV function in systolic heart failure patients has previously been limited to studies comparing only the resting LVEF in patients with and without known DM. Most of these studies reported no significant difference in this parameter. We comprehensively assessed both glucose metabolism and LV function at rest and during LDE shortly after a first visit in a heart failure clinic. Echocardiographic parameters reflecting LV systolic and diastolic function, filling pressure as well as contractile reserve, and with known associations with prognosis, were found to be impaired in both patients with known and newly diagnosed DM. Additionally, in patients without known DM we found an independent inverse correlation of LV contractile reserve with increasing 2hPG and HOMA-IR, but not with HbA1c. Apart from illustrating a negative impact of abnormal glucose metabolism on LV function even in patients without overt DM, these findings suggest that LV dysfunction in patients with known DM may be underestimated when compared to a control population where screening for unrecognized DM is not attempted as opposed to comparison with normal glucose tolerance patients. Presumably this is the explanation why previous studies did not detect such reductions in resting LVEF among DM patients. Furthermore, the evaluation of LV contractile function during inotropic stimulation expand the characteristics of the

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systolic dysfunction associated with abnormal glucose metabolism, as the reduced LVEF in these patients was markedly accentuated during LDDE. The reduction in contractile reserve may constitute an important link between abnormal glucose metabolism, symptom severity, and heart failure mortality. Two recent reports from the VALIANT and ASPIRE trials also reported echocardiographic LV parameters beyond the resting LVEF in patients with or without DM and with a recent myocardial infarction complicated by reduced LVEF. In these studies known DM was associated with diastolic dysfunction and with concentric remodeling rather than systolic dysfunction. The discrepancy between these findings and ours may be explained by differences in heart failure severity and by the lack of OGTT testing resulting in a bias towards equality of the glycemic groups.

6.3 Glucose metabolism and exercise capacity in chronic systolic heart failure

In agreement with previous reports we found exercise capacity assessed by 6MWD to be reduced in both patients with DM and less severe abnormal glucose metabolism. In addition we found that 2hPG had the second-strongest correlation with 6MWD (after age) in patients without known DM. Although E/e' and LDDE LVEF were correlated with 6MWD, these LV measures did not explain the association between glucose metabolism and exercise intolerance. Thus, reduced exercise capacity is present in patients with abnormal glucose metabolism, even below the diabetic threshold, and this is not explained by more extensive LV dysfunction but to some degree by an unfavorable clinical status in these patients compared to those with normal glucose tolerance. Presumably non-cardiac factors that we were not able to control for determined the differences in exercise capacity. Impairment of vascular and skeletal muscle function is common in DM patients and affects exercise capacity, and may instead explain the residual confounding beyond the clinical determinants in our analyses.

6.4 Glucose metabolism and the effect of heart failure treatment on the severity of heart failure and left ventricular function

Whether a reduced response to treatment contributes to the excess mortality of diabetic heart failure patients has not been prospectively evaluated. Most clinical trials report a reduction in mortality similar to patients without known DM. However, patients in such trials are often relatively selected, and only the effect of a single drug is usually considered. The conclusions, therefore, may not apply to a more unselected and older outpatient population receiving treatment in a heart failure clinic, where a guideline driven multi-disciplinary approach constitutes the core of intervention. Because of a small sample size and limited follow-up time, we aimed at evaluating treatment efficacy by using changes in LV function and NT-proBNP as surrogate markers of prognosis. Such short-term changes have been shown to predict longer-term outcomes. A notable finding was that patients with the most adverse baseline status in general had the largest improvement in LV function and decrease in NT-proBNP, and all outcome parameters were therefore adjusted for baseline values to avoid bias. After six months of treatment, patients with known and newly detected DM were up-titrated to lower doses of ACE-I or ARB. Yet, the response to treatment with respect to clinically significant improvements in resting LV function and NT-proBNP was unaffected by glycemic status. Conversely, the likelihood of an increase in LDDE LVEF was much smaller in known DM patients, but not influenced by HbA1c, fasting-, or postprandial glucose concentrations in those without known DM. Although we cannot conclude on the impact on mortality, patients with abnormal glucose metabolism, including those with known DM, obtain treatment-induced improvements in important prognostic markers comparable to that of normal glucose tolerance patients, which likely translate into prolonged survival. However, the more severe heart failure phenotype and poor function of the LV at baseline persisted to some extent in patients with known DM, who had lower quality of life and exercise capacity, higher NT-proBNP concentrations, and poorer LV function at follow-up. A poor baseline status with similar treatment effects on LV function in patients with and without DM were also observed in the VALIANT and ASPIRE studies. These and our findings provide a possible explanation for some of the risk associated with abnormal glucose metabolism, and underscore the importance of an early diagnosis of heart failure in patients with abnormal glucose metabolism followed up by aggressive adherence to evidence based treatment.

6.5 Limitations

The associations between glucose metabolism and outcomes found in the current studies should not be interpreted as causal. OGTT-detected hyperglycemia could be caused by, as well as a cause of, increased heart failure severity.

Data on exercise capacity and LDDE were unavailable in the mortality study and mortality was low due to a short follow-up period in the LDDE studies. We are therefore unable to directly assess whether and to what extent increased LV dysfunction beyond the resting LVEF and exercise intolerance contributed to the increased mortality in DM patients.

We did not measure vascular functions such as flow-mediated vasodilatation, coronary flow reserve, or other markers of endothelial dysfunction, which could be relevant for explaining exercise intolerance and LV dysfunction in DM patients. Neither did we register the prevalence of musculoskeletal disorders.

We cannot conclude on the prognostic power of IGT and newly diagnosed DM versus normal glucose tolerance due to low sample size. We chose to dichotomize change in NT-proBNP from baseline to follow-up as an at least 30% decrease. A higher cut-off value may be required to fully exclude changes solely due to analytic variation, but the number of patients with a positive response would have been too low. Therefore in order to increase power, we substituted the group comparison of newly diagnosed DM, IGT, and normal glucose tolerance with analysis of 2hPG as a continuous variable with respect to the likelihood of improvement in LVEF and NT-proBNP. In general the sample size did not allow subgroup analyses, for instance investigation of difference in predictive power of DM or 2hPG in patients with and without ischemic heart disease.

Study IV showed that infusion of dobutamine at rates of 20 µg/kg/min increased cardiac output significantly more than a rate of 10 µg/kg/min, which was used in study II and III, without clinically important increases in heart rate and vascular resistance. Thus, higher doses of dobutamine may be preferable in assessing contractile reserve in chronic heart failure patients not withholding beta-blockers.
7. Conclusions

1. The prevalence of unrecognized abnormal glucose metabolism is high in outpatients with chronic systolic heart failure, and many are misclassified if an OGTT is omitted. The prevalence of known and newly detected diabetes was found to be 34%.

2. Heart failure outpatients with diabetes, known and OGTT-detected, have an almost two-fold increase in long-term mortality compared to patients without diabetes.

3. Abnormal glucose metabolism is associated with a poor left ventricular contractile reserve and reduced exercise capacity in patients with newly diagnosed chronic systolic heart failure.

4. The benefit of guideline-driven treatment in a heart failure clinic with regard to improvement in resting systolic LV function and reduction in NT-proBNP is similar in patients with and without abnormal glucose metabolism. However, known diabetes patients do not obtain improved contractile reserve.

5. Low-dose dobutamine echocardiography is feasible and safe in chronic systolic heart failure patients. Echocardiographic measures of systolic function correlates closely with the increased cardiac output observed during inotropic stimulation, but E/e' does not correlate with LV filling pressure during dobutamine infusion.
8. Clinical implications and future studies

Our results strengthen the recommendation of OGTT screening in outpatients with chronic systolic heart failure for risk stratification purposes. This test is feasible, safe, and identifies a substantial proportion of patients with IGT and DM who would be considered normal with respect to glucose metabolism if classified by HbA1c or FPG. Although we are unable to definitely conclude on the impact on mortality, it seems that these patients are at increased risk. However, no specific therapeutic options currently exist to lower this excess risk in IGT and DM patients identified by OGTT screening. Conversely, since the life expectancy of heart failure patients has risen significantly in recent decades, the institution of antidiabetic treatment in patients with severe abnormal glucose metabolism may prevent cases of blindness and end-stage renal failure.

A frank DM diagnosis at the time of heart failure debut warrants efforts to achieve maximally tolerated doses of conventional pharmacological heart failure therapy, as this treatment appears effective in the improvement of resting LV systolic function and probably in reducing mortality in these patients. Whether asymptomatic DM patients should be routinely screened for left ventricular dysfunction for the early initiation of heart failure therapy, and by which methods, should be investigated in future studies.

Interventional studies targeting overall glycemic burden has mainly proved unsuccessful in ameliorating the negative prognostic impact of DM on macrovascular disease. Instead, some evidence of a beneficial effect of the specific lowering of postprandial glucose concentration was found in the somewhat criticized STOP-NIDDM trial. Also, metformin treatment has been shown to improve diastolic function and with fewer cardiovascular events in the UKPDS trial. Thus postprandial glucose and insulin resistance should be further explored as treatment targets in heart failure patients.

More recently, the identification of molecular mechanisms linking DM and insulin resistance with unfavorable alterations in LV structure and function have been identified, and these could serve as treatment targets in the prevention of DM related LV dysfunction. One target is the cleavage of advanced glycation end products, which exists in large concentrations in DM patients and is related to myocardial stiffening and diastolic dysfunction, but preliminary results are somewhat discouraging. Other potential treatments include reduction of oxidative stress by antioxidants and fibrosis prevention by endothelin receptor antagonists. Infusion of glucagon-like peptide-1, an incretin which increases insulin production and –sensitivity, has been associated with improved LV ejection fraction and functional status and may be a promising new agent in diabetic heart failure patients.

However, at present the primary prevention of abnormal glucose metabolism may be the best option to avoid the excess incidence of heart failure and mortality related to these conditions. The progression from IGT to DM has been shown to be delayed by the angiotensin receptor blocker Valsartan in patients with risk factors for CVD, although this did not reduce the risk of cardiovascular events.
9. Summary

This PhD thesis is based on four original manuscripts conducted at the Department of Cardiology and Endocrinology, Frederiksberg University Hospital and Department of Cardiology, Copenhagen University Hospital, Rigshospitalet.

Background
Patients with type-2 diabetes have an increased risk of developing of chronic systolic heart failure and diabetes increases mortality and reduces exercise capacity in these patients. Abnormal glucose metabolism, even below the diabetic threshold, has also been associated with the development of heart failure and with an adverse prognosis in patients with ischemic heart disease. It is however unknown if the poor prognosis in patients with abnormal glucose metabolism is related to reduced left ventricular function or lower treatment efficacy.

Objectives
In outpatients with chronic systolic heart failure

1. To assess the prevalence of unrecognized diabetes and impaired glucose tolerance by oral glucose tolerance testing.
2. To assess the impact of abnormal glucose metabolism on mortality
3. To investigate the association between glucose metabolism and left ventricular function.
4. To investigate the association between glucose metabolism and exercise capacity.
5. To evaluate the effects of treatment in an outpatient heart failure clinic on disease severity and left ventricular function in relation to glucose metabolism.
6. To investigate the hemodynamic response determined by right heart catheterization and the correlations with LV systolic function, diastolic function, and filling pressure during low-dose dobutamine echocardiography.

Methods
Patients with newly diagnosed chronic systolic heart failure and a left ventricular ejection fraction ≤ 45% were consecutively recruited from an outpatient heart failure clinic. Patients without a known diabetes diagnosis were examined by a standardized oral glucose tolerance test and classified by WHO criteria into groups: normal glucose tolerance, impaired glucose tolerance, newly detected diabetes. The prevalence of abnormal glucose metabolism was assessed in 309 patients, and all-cause mortality was registered during a median follow-up time of 1.6 years. In 161 patients resting left ventricular function and contractile reserve were characterized by low-dose dobutamine echocardiography, exercise capacity was evaluated by a 6-minute walking distance test, and the severity of heart failure assessed by NT-proBNP concentrations. These tests were repeated after 6 months in surviving patients without major ischemic events.

Fourteen patients underwent simultaneous right heart catheterization and low-dose dobutamine echocardiography.

Results
Known diabetes affected 20% and newly detected diabetes and impaired glucose tolerance was present in more than 40% of the remaining patients. All-cause mortality in patients with known or newly detected diabetes was increased 1.9 times compared to patients without diabetes.

Abnormal glucose metabolism was independently associated with a reduced left ventricular contractile reserve and exercise intolerance in outpatients with chronic systolic heart failure, but the poor left ventricular function did not seem to explain the exercise intolerance. After six months treatment in the heart failure clinic, patients with newly detected and known diabetes received lower doses of angiotensin converting enzyme inhibitors, but nevertheless experienced a large improvement in resting left ventricular function (from 31±9.7% to 38.5±9.0%, P=0.005) and decrease in NT-proBNP (from 1109 pg/ml to 863 pg/ml, P=0.015), that did not differ significantly from the changes in patients with normal glucose tolerance. The likelihood of an increase from baseline to follow-up in left ventricular ejection fraction during inotropic stimulation was lower in patients with known diabetes. Left ventricular filling pressure remained higher and exercise capacity remained lower in known and newly diagnosed diabetes patients.

Echocardiographic estimates of left ventricular systolic function were closely correlated with invasively estimated cardiac output during low-dose dobutamine echocardiography. Echocardiographic left ventricular filling pressure estimates during dobutamine-infusion were not associated with the pulmonary capillary wedge pressure.

Conclusions
A substantial proportion of chronic heart failure patients were found to have unrecognized abnormal glucose metabolism. The presence of diabetes, known or detected by oral glucose tolerance testing, was associated with a high mortality rate, reduced left ventricular contractile reserve, and exercise intolerance. Guideline driven treatment in a heart clinic had comparable beneficial effects on disease severity and resting left ventricular function irrespective of glycemic status, but not on left ventricular ejection fraction during inotropic stimulation, where known diabetes patients failed to obtain an improvement.
Baggrund
Patienter med type-2 diabetes har forøget risiko for udvikling af kronisk systolisk hjertesvigt og medfører hos disse patienter øget mortalitet og nedsat fysisk kapacitet. Ud over manifest diabetes har forstyrrelser i glukosemetabolismen detekteret med en oral glukose tolerance test, selv under den diagnostiske grænse for diabetes, også vist sig at være associeret med øget risiko for hjertesvigt samt at have prognostisk betydning ved iskæmisk hjertesygdom. Det er ukendt hvorvidt den dårlige prognose hos patienter med abnorm glukosemetabolisme kan skyldes dårligere venstre ventrifikelfunction eller nedsat behandlingseffekt.

Formål
Hos ambulante patienter med kronisk systolisk hjertesvigt

1. At bestemme prævalensen af uopdaget diabetes og nedsat glucose tolerance
2. At vurdere betydningen af abnorm glukose metabolism for dødeligheden.
3. At undersøge sammenhængen mellem abnorm glukose metabolisme og venstre ventrifikelfunction.
4. At undersøge sammenhængen mellem abnorm glukose metabolisme og fysisk kapacitet.
5. At evaluere effekten af behandling i en hjertesvigtiklinik på sværhedsgrad af hjertesvigt og venstre ventrifikelfunktion i relation til glukosemetabolisme.
6. At undersøge invasivt bestemt hæmodynamiske respons og sammenhæng med venstre ventrikel systolisk og dia-stolisk funktion samt fyldningstryk vurderet under lavdo-sis dobutamin-ekkokardiografi.

Metoder

Resultater
Kendt diabetes var diagnosticeret hos 20% og nyopdaget nedsat glukose tolerance og diabetes blev konstateret hos mere end 40% af de resterende patienter. Risikoen for død af enhver årsag var 1.9 gange højere blandt patienter med kendt eller nyopdaget diabetes.

Abnorm glukose metabolisme var uafhængigt associeret med nedsat venstre ventrikel kontraktile reserve og fysisk kapacitet hos patienter med nykonstateret kronisk systolisk hjertesvigt, men den nedsatte funktion af venstre ventrikel synes ikke at kunne forklare den nedsatte fysiske kapacitet. I løbet af 6 måneders behandling i hjertesvigtiklinik opnåede patienter med kendt og nyopdaget diabetes lavere doser af angiotensin-converterende enzym hæmme-re, men betydelige forbedringer i hvilende venstre ventrikel ud-drivningsfraktion (fra 31±9.7% til 38.5±9.0%, P=0.005) og redukti-on i NT-proBNP koncentration (fra 1109 pg/ml til 863 pg/ml, P=0.015), der ikke var signifikant forskellig fra de opnåede resulta-ter hos patienter med normal glucose tolerance. Derimod var sandsynligheden for at opnå forbedret venstre ventrikel uddrivningsfraktion under dobutamin stimulation lavere blandt patienter med kendt diabetes. Efter endt opfølgingstid forblev venstre ventrikels estimerede fyldningstryk forhøjet og den fysiske funktionsevne reduceret hos patienter med kendt og nyopdaget diabe-tes.

Ekkokardiografiske parametre for venstre ventrikel systole funktion var stærkt associeret med invasivt bestemt minutvolumen under lavdosis dobutamin-ekkokardiografi. Ekkokardiografiske estimer af venstre ventrikel fyldningstryk var ikke korreleret til det pulmonale indkilingstryk under dobutamininfusion.

Konklusioner
11. References


Oral glucose tolerance testing in an outpatient heart failure clinic reveals a high proportion of undiagnosed diabetic patients with an adverse prognosis

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Aims

We evaluated the applicability and prognostic importance of oral glucose tolerance testing (OGTT) among outpatients with systolic heart failure (SHF).

Methods and results

Consecutive patients with SHF and left ventricular ejection fraction (LVEF) ≤ 45% referred to a heart failure clinic (n = 413) were included in this study. An OGTT was conducted in patients without a history of diabetes. Information on NYHA class, aetiology of SHF, LVEF, treatment, and biochemical parameters were collected at baseline. The survival status was obtained after a median follow-up time of 591 days. Of the 413 patients, 82 (20%) had known diabetes. Of the remaining 331 patients, 227 (69%) agreed to undergo an OGTT. Among the tested subjects, 136 (60%) were classified as having normal glucose tolerance (NGT), 51 (23%) impaired glucose tolerance (IGT), and 40 (18%) newly diagnosed diabetes. Assuming a similar prevalence of unrecognized diabetes among the patients who refused OGTT, the prevalence of diabetes in the total population was 34%. If only fasting blood glucose had been used, 16 of the 40 newly diagnosed diabetic patients would have been undiagnosed. During follow-up, 24 (29%) patients with known diabetes, 6 (15%) of the newly diagnosed diabetic patients, 9 (18%) of those with IGT, and 13 (9%) patients with NGT died. Patients with diabetes had higher mortality rate compared with non-diabetic patients (multivariate hazard ratio 1.89 (1.02−3.59); P = 0.047).

Conclusion

It is feasible to perform diabetes screening using OGTT in outpatients with SHF. A substantial proportion of patients tested were found to have unrecognized diabetes. The presence of diabetes was associated with a higher mortality rate.

Keywords

Heart failure • Oral glucose tolerance test • Diabetes prevalence • Mortality

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Abnormal glucose metabolism is associated with reduced left ventricular contractile reserve and exercise intolerance in patients with chronic heart failure


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Aims
To investigate the associations between glucose metabolism, left ventricular (LV) contractile reserve, and exercise capacity in patients with chronic systolic heart failure (HF).

Methods and results
From an outpatient HF clinic, 161 patients with systolic HF were included (mean age 70 ± 10 years, 69% male, 59% had ischaemic heart disease, mean LV ejection fraction (LVEF) 37 ± 9%). Thirty-four (21%) patients had known diabetes mellitus (DM). Oral glucose tolerance testing (OGTT) classified patients without a prior DM diagnosis as normal glucose tolerance (NGT), impaired glucose tolerance or new DM. All patients completed low-dose dobutamine echocardiography (LDDDE) and 154 patients a 6-min walking distance test (6MWD). Compared with patients with NGT, patients with known DM had lower resting LVEF (33.4 vs. 39.1%, P < 0.05) and higher E/e’ (13.9 vs. 11.4, P < 0.05). During LDDDE, an increase in LVEF could be observed in all glycemic groups (mean 8.2% absolute increase), but the contractile reserve was lower in patients with known DM (−5.4%, P = 0.001) and new DM (−3.5%, P = 0.035) compared to patients with NGT. 6MWD was lower in known DM (349 m) and new DM (379 m) compared with NGT (467 m) (P < 0.001). Differences in clinical variables, resting echocardiographic parameters or contractile reserve, did not explain the exercise intolerance related to diabetes.

Conclusion
Diabetes, known or newly detected by OGTT, is independently associated with reduced LV contractile reserve and exercise intolerance in outpatients with systolic HF. These findings may offer one explanation for the excess mortality related to diabetes in HF.

Keywords
Heart failure • Diabetes mellitus • Glucose metabolism • Contractile reserve • Exercise capacity • Dobutamine stress echocardiography

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Effects of Treatment in a Heart Failure Clinic on Disease Severity and Left Ventricular Function in Relation to Glucose Metabolism

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Abstract

AIMS: To assess whether effects of medical treatment on left ventricular (LV) function and severity of heart failure (HF) are influenced by glycemic status in patients with HF.

METHODS AND RESULTS: Glucose metabolism was characterized in 136 outpatients with HF (LVEF ≤ 45%) by a known diabetes (DM) diagnosis (N=26, 19%) or by glucose tolerance testing (N=110) detecting new DM in 24 (18%) and impaired glucose tolerance (IGT) in 22 (16%). At baseline and after 6 months of treatment LV function was evaluated by low-dose dobutamine echocardiography (LDDE), and severity of HF by NT-proBNP, quality of life score, and 6-minute walk test. At baseline known DM patients had reduced LV systolic function and more severe HF compared to normal glucose tolerance (NGT) patients. IGT/new DM patients were intermediately affected. At follow-up, known DM patients achieved an increase in resting LVEF (+6.9±10.8%, P=0.005) and decrease in NT-proBNP (-247 pg/mL, P=0.02), but had a low likelihood for improvement in LDDE LVEF. IGT/new DM patients obtained treatment benefits comparable to NGT patients.

CONCLUSIONS: HF treatment confers beneficial effects on HF symptom severity and resting LV function irrespective of glycemic status, but not on LVEF during inotropic stimulation, where DM patients failed to improve.

Keywords: Heart failure, glucose metabolism, left ventricular function, symptom severity
Hemodynamic Response During Low-dose Dobutamine Infusion in Patients with Chronic Systolic Heart Failure: Comparison of Echocardiographic and Invasive Measurements

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Abstract

Aims: It is incompletely established if resting estimates of LV diastolic function, e' and the E/e' ratio, reflects the hemodynamic changes during LDDE in patients with chronic systolic heart failure (CHF). We investigated if left ventricular (LV) systolic shortening velocity (s'), diastolic lengthening velocity (e'), and LV filling pressure estimate (E/e') during low-dose dobutamine echocardiography (LDDE) reflect invasive measures of cardiac output and pulmonary capillary wedge pressure (PCWP) in stable CHF outpatients.

Methods and results: Fourteen CHF patients (age 65±8 years, 8 (57%) male, mean LVEF 36±8%) underwent simultaneous tissue Doppler echocardiography and invasive measurements of cardiac output and PCWP by right heart catheterization at rest and during dobutamine infusion at rates of 10 and 20 µg/kg/min. Cardiac output increased from rest to peak dobutamine (4.9±1.2 L/min to 6.6±2.0 L/min, P<0.001) and a strong correlation with the peak systolic tissue velocity (s') was found at rest and during dobutamine stimulation. Both the early diastolic mitral inflow (E) and LV lengthening (e') velocities increased during LDDE leaving the E/e' ratio unchanged. Although mean PCWP was also unchanged from rest to peak dobutamine (16.6±8.3 vs. 14.2±9.2, P=0.25), a correlation between E/e' and PCWP could only be found at rest (R=0.64, P=0.014).

Conclusions: The LV systolic shortening velocity is closely associated with cardiac output during LDDE in CHF patients. Dobutamine stimulation increases early diastolic mitral inflow and lengthening velocities, but the E/e' ratio does not reflect PCWP during LDDE, which warrants caution in converting changes in E/e' into changes in LV filling pressure.
Ph.D. thesis

Glucose Metabolism in Chronic Systolic Heart Failure
Relation to Left Ventricular Function, Exercise Capacity, and Mortality

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