

**MYOCARDIAL CONTRACTION FRACTION, DIABETES AND HEART  
FAILURE: THE MULTI ETHNIC STUDY OF ATHEROSCLEROSIS.**

BY

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## ABBREVIATIONS

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	Angiotensin Converting Enzyme
ACR	Albumin-creatinine ratio
ADA	American Diabetes Association
ANOVA	Analysis of variance
BMI	Body mass Index
CAC	coronary artery calcium
CT	Computed Tomography
CV	Cardiovascular
CVD	Cardiovascular disease
DCM	Diabetic cardiomyopathy
DD	Diastolic dysfunction
DM	Diabetes mellitus
EDV	End-diastolic volume
EF	Ejection fraction
ESV	End-systolic volume
HbA1c	Glycated hemoglobin
HDL	High density lipoprotein
HF	Heart Failure
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IMT	Intima-media thickness
LV	Left ventricular
LVM	Left ventricular mass

LVH	Left ventricular hypertrophy
MCF	Myocardial contraction fraction
MESA	Multiethnic study of atherosclerosis
MRI	Magnetic resonance imaging
MV	Myocardial volume
MWSF	Mid-wall shortening fraction
NFG	Normal fasting glucose
NIDDK	National Institute of Diabetes and Digestive and Kidney disease
RAAS	Renin angiotensin aldosterone system
SV	Stroke volume
SF	Shortening fraction
T2DM	Type 2 diabetes mellitus
3D	Three dimensional

## ABSTRACT

**Objective:** We sought to investigate differences in myocardial contraction fraction (MCF) by glucose metabolism status and determine whether reduced MCF is predictive of incident heart failure (HF) in the Multi-Ethnic study of Atherosclerosis, a cohort study of 6814 adults aged 45-84 without prior cardiovascular (CV) disease.

**Background:** Diabetic individuals have altered cardiac structure and function which increases their risk for HF. Myocardial contraction fraction is an echocardiographic measure of fractional shortening recently applied to cardiovascular magnetic resonance (CMR).

**Methods:** We included 4991 participants who had CMR data for whom diabetes status could be ascertained. Left ventricular (LV) volumes and mass (LVM) were calculated by the summation of disks method from cine short axis images. MCF was calculated as LV stroke volume/LV myocardial volume. Diabetes (DM) and impaired fasting glucose (IFG) were defined according to the 2003 ADA established criteria. Linear regression was used to determine the potential association between MCF and diabetes status, after accounting for demographics and CV risk factors. Cox models were used to assess MCF, EF and LVM as predictors of HF adjusting for the above variables.

**Results:** MCF was lower in those with DM or IFG ( $p < 0.0001$ ) compared to subjects with normal fasting glucose (NFG). After full adjustment, those with IFG or DM exhibited a lower MCF [IFG -0.02 (95%CI -0.03, -0.01) DM -0.02 (95%CI -0.03, -0.001)] relative to those with NFG, while there was no significant difference in EF and LVM between glucose categories. Among diabetics 39.1% were in the 1<sup>st</sup> MCF quartile compared to 27% in the 1<sup>st</sup> EF quartile ( $p < 0.0001$ ). There were 96 cases of incident HF. Compared to the 4th quartile, the 1st MCF quartile was associated with HF [HR 2.1; 95%CI 1.0, 4.3] as was 1st EF quartile [HR 2.9; 95%CI 1.6, 5.3] and 4th quartile LVM [HR 4.9; 95%CI 1.9, 12.1].

**Conclusion:** After accounting for demographics and CV risk factors, MCF predicts future HF, and could better identify – than EF and LV mass – diabetic persons at risk for HF

## CHAPTER ONE

### INTRODUCTION

Heart Failure (HF) is a major cause of morbidity and mortality in the United States and its prevalence continues to rise (1-3). It has become a frequent manifestation of cardiovascular disease (CVD) among persons with type 2 diabetes mellitus (T2DM) (4, 5).

As the prevalence of T2DM increases, it will likely emerge as one of the principal causes of heart failure in the United States (6-8). The association between diabetes mellitus (DM) and HF can be partly attributed to associated cardiovascular risk factors common among those with diabetes (9). However, diabetic individuals remain at increased risk of heart failure after adjusting for these concomitant risk factors. Diabetic persons are at increased risk of developing heart failure following myocardial infarction (10) but they're equally susceptible to heart failure of non ischemic origin (11). Currently, there is a clear recognition of diabetic cardiomyopathy (DCM) as a distinct disease process partly responsible for the increased risk of HF in diabetic patients (12).

At present, diabetic cardiomyopathy is essentially seen as a set of pre-HF abnormalities that may be seen on echocardiography including increased left ventricular mass (LVM) and impaired diastolic function (13-15).

Previously, Bertoni et al have shown that ethnicity-specific differences in left ventricular mass, end-diastolic volume (EDV) and stroke volume (SV) are associated with abnormal glucose metabolism and are independent of subclinical cardiovascular disease in the MESA cohort (16). However there was no significant difference in ejection fraction (EF) between individuals with normal fasting glucose, impaired fasting glucose and diabetes. Reduced EF has been established as a predictor of cardiovascular (CV) morbidity and mortality (17, 18) and is a predictor of incident HF. However, reduced ejection fraction may not predict all HF cases as many patients with HF symptoms have "preserved" left ventricular (LV) EF (19, 20).

Using 3D echocardiography, a new volumetric index, myocardial contraction fraction (MCF) defined as the ratio of stroke volume (SV) to myocardial volume (MV) was used to discriminate between hypertensive patients with LV hypertrophy and athletes with physiologic hypertrophy (21). In the MCF parameter, SV is the amount by which the myocardium contracts (i.e., shortens) during systole relative to the total MV, although the myocardium itself has not undergone a reduction in volume (22). During systole the myocardium shortens and thickens, reducing its contained volume by the amount of the SV. Therefore, the SV is a measure of the amount of shortening and thickening that has occurred, and its ratio to MV is an index of the fractional shortening of the myocardium in volumetric terms. Because this ratio removes the geometric influence of chamber volume (end-diastolic volume) from the denominator of the shortening expression, it was hypothesized that it may be a more useful measure of myocardial performance and could better delineate differences in ventricular function in patients with different degrees and types of hypertrophy than conventional measures (21). By eliminating chamber volume from the shortening assessment, the MCF expresses the shortening relationship only in terms of that which shortens the myocardium. As a dimensionless index analogous to EF, it easily permits comparison of myocardial shortening between subjects. A decrease in MCF would indicate abnormal myocardial shortening induced either by hypertrophy or by intrinsic myocardial disease that reduces stroke volume (21). Also, given that  $MV = LVM/1.05$  (the specific gravity of the myocardium), MCF can also be expressed as  $1.05 \times [(EDV/LVM) - (ESV/LVM)]$ , where ESV is end-systolic volume. Now, we know that EDV/LVM is the inverse of LV concentricity in end-diastole and ESV/LVM is a similar parameter in end-systole. This suggests that apart from the quantity 1.05, MCF could also be seen as a measure of LV geometry.

The mean MCF for normal adults included in the study by King et al was  $0.44 \pm 0.07$ ; patients with hypertensive hypertrophy had lower values ( $0.33 \pm 0.04$ ) while the athletes had higher values ( $0.55 \pm 0.05$ ). We are unaware of the application of MCF to MRI, however the principles should

be the same, as volumes (and consequently EF) are calculated the same way using MRI as for echocardiography (although with greater precision with MRI).

Given that myocardial contraction fraction is an indicator of abnormalities in ventricular function and geometry – both present in diabetic cardiomyopathy – it is potentially a better indicator of DCM and heart failure risk than ejection fraction. It is not known whether MCF differs by diabetes status or if it is predictive of heart failure. MESA will provide an opportunity to investigate these issues in a large multiethnic cohort. We therefore aim to use the MESA cohort to: Investigate differences in MCF between subjects with normal fasting glucose (NFG), impaired fasting glucose (IFG) and diabetes and determine whether reduced MCF is predictive of incident HF.

Prior to undertaking the proposed research, a review of the current literature of the epidemics of diabetes and heart failure and the pathologic basis of diabetic cardiomyopathy will be presented. In addition, this document will discuss abnormalities in LV function and structure in diabetes patients and information pertaining to the novel volumetric index of myocardial shortening – myocardial contraction fraction.

## **1. Burden of Diabetes**

### **1.1 Prevalence and risk factors**

The diabetes epidemic has continued unchecked into the 21st century with an extraordinary toll on the U.S. population through its acute and chronic complications, disability, and premature death (23). According to the 2007 NIDDK statistics (National Institute of Diabetes and Digestive and Kidney diseases), 10.7% of the adult population aged  $\geq 20$  years have diabetes (23.5 million Americans) and in adults  $\geq 60$  years the prevalence stands at 23.1% (24). Data from the National Health Interview Survey indicates that the prevalence of diabetes has increased 4-8 fold over the last half century, an increase seen across all demographic categories including sex, age and ethnicity (25). In 2007, diabetes cost the US in excess of \$174 billion (26) and this figure is expected to rise sharply given that the overall prevalence of diabetes is expected to reach 28% by 2050 (27). The rising prevalence of overweight and obesity and sedentary lifestyle are well-recognized as the drivers of the epidemic of type 2 diabetes in the US together with aging and an increase in the population of minority groups that are at increased risk for diabetes (28, 29).

### **1.2 Diabetes and cardiovascular disease.**

Diabetes is known to be a major risk factor for cardiovascular disease (CVD), which largely contributes to the decreased life expectancy and increased mortality in persons with diabetes when compared with the general population (24, 30).

Despite recent advances in knowledge, several important questions regarding prevention of CVD in diabetes remain unanswered, including the benefits of intensive, near-normal glycemic control; comprehensive therapy for diabetes-related dyslipidemia; and optimal blood pressure control (31). The early interruption of the intensive glucose lowering arm of the ACCORD glycemic trial for increased all-cause mortality coupled with the fact that the results of the blood pressure and

lipid trials left more unsettled queries suggests that further research is required to fully resolve the challenge of preventing CVD in persons with diabetes (32-34).

## **2. Burden of Heart Failure**

### **2.1 Prevalence**

Heart Failure (HF) is a major cause of morbidity and mortality in the United States and its prevalence continues to rise (1-3). It has thus become a major public health concern especially for elderly Americans (35, 36) and has been described as a “new” or “emerging” epidemic for the 21<sup>st</sup> century (37, 38). Currently 5.2 million Americans (2.5%) are estimated to have heart failure (39). In 2007 the estimated direct and indirect costs of heart failure in the U.S. was \$33.2 billion (39).

### **2.2 Risk factors**

It is established that the incidence of HF rises sharply with age (40). The rate of HF hospitalizations in the US has increased progressively over the past decades with the aging of the population (41). Also, African American ethnicity has been suggested as an independent risk factor for heart failure (HF) (42); they have higher mortality and hospitalization rates compared with white populations (43). Using data from the Multi-Ethnic Study of Atherosclerosis (MESA), Bahrami et al showed that the higher risk of incident HF among African Americans was related to differences in the prevalence of hypertension and diabetes mellitus as well as socioeconomic status (44). The mechanisms of HF also differed by ethnicity; interim myocardial infarction had the least influence among African Americans, and higher left ventricular mass had the greatest effect among Hispanic and white participants (44).

Hypertension, cardiovascular disease (including coronary artery disease and stroke), valvular heart disease, and atrial fibrillation are well established risk factors for HF (45, 46). Over the last

decades, diabetes has also become well recognized as a major risk factor for HF and it is an independent risk factor for increased mortality among individuals with heart failure (6, 7, 47).

### **3. Diabetes and Heart Failure**

#### **3.1 Heart Failure risk in Persons with Diabetes**

In the Framingham study of an unselected cohort of 5209 individuals, the frequency of HF in diabetic males was over twice that of non-diabetic subjects, whilst female diabetic patients were over five times more susceptible to heart failure and this risk was independent of age, hypertension, obesity, coronary artery disease and hyperlipidemia (47). The Cardiovascular Health Study and Euro Heart Failure Surveys also suggested that the presence of diabetes may independently increase the risk of developing incident heart failure (7, 48, 49). Furthermore, diabetic patients have an increased likelihood of developing heart failure following myocardial infarction and once established the outcome is worse than for non-diabetics (10).

#### **3.2 Diabetic Cardiomyopathy**

##### **3.2.1 Definition and Natural History**

Currently, there is a clear recognition of diabetic cardiomyopathy as a distinct disease process partly responsible for the increased risk of HF in diabetic patients (12). This condition was originally described by Rubler et al in 1972 (50) and has subsequently been confirmed by large epidemiological studies (47). Diabetic cardiomyopathy (DCM) could be seen as the presence of abnormal myocardial performance or structure in the absence of epicardial coronary artery disease, hypertension or significant valvular disease (51). Often the term is used to describe pre-clinical abnormalities like increased left ventricular mass and diastolic dysfunction observed on echocardiography (13-15). The natural history consists of a latent subclinical period, during which cellular structural insults lead initially to diastolic dysfunction (with concomitant atrial

dilatation) and left ventricular hypertrophy and eventually systolic dysfunction (12). Later in the disease evolution, these structural changes act synergistically with the vascular consequences of hypertension and cardiac ischaemia to precipitate overt clinical deterioration.

### **3.2.2 Pathology and Pathophysiology**

The classical pathologic lesions seen in DCM include myocardial hypertrophy, interstitial fibrosis with collagen deposition, capillary endothelial changes, capillary basal laminae thickening, and alterations in the myocardial microvascular circulation (52-54). Several pathophysiologic mechanisms have been proposed to explain the structural and functional changes associated with DCM: they include - but are not limited to - the deleterious effects of hyperglycemia, excess free fatty acids, reactive oxygen species, the renin angiotensin aldosterone system (RAAS), inflammatory cytokines and microangiopathy (51, 54-56). Their interplay is complex since they act in parallel and synergistically as shown in figures 1 and 2 (54, 56).

### **3.2.3 Risk factors and treatment options**

A report from the Studies of Left Ventricular Dysfunction (SOLVD) trial indicated that diabetes is an independent risk factor for increased morbidity and mortality in both symptomatic and asymptomatic patients with heart failure (57). Furthermore, T2DM was associated with an increased risk of HF and death in patients with an acute myocardial ischemic event (58, 59). This underlines the importance of the prevention of HF in the diabetic population across screening and risk stratification of asymptomatic patients. Epidemiologic evidence suggests increased blood pressure, worse glycemic control (higher hemoglobin A1c) and obesity are risk factors for HF among adults with T2DM (5). According to the AHA/ACC Heart Failure guidelines tight control of blood pressure, lipids, and glycemia and the use of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers are useful preventive strategies (60); however no prevention trials in persons with diabetes have been done. Also, novel diabetes-specific therapies

for DCM – including advanced glycation end product inhibitors e.g. aminoguanidine and advanced glycation end product cross-link breakers e.g. alanine aminotransferase 711 – which are likely to succeed at earlier stages of myocardial dysfunction are being developed. This underscores efforts to develop strategies for early detection; especially with conventional and novel imaging techniques since these newer drugs are likely to be more effective in the earlier stages of DCM. The proposed study suggests a novel volumetric index (which can be calculated using data from 3D echocardiography or cardiac MRI) which may be a better indicator for diabetic cardiomyopathy - and heart failure risk – than ejection fraction.

Figure 1: Pathophysiologic mechanisms involved in Diabetic Cardiomyopathy

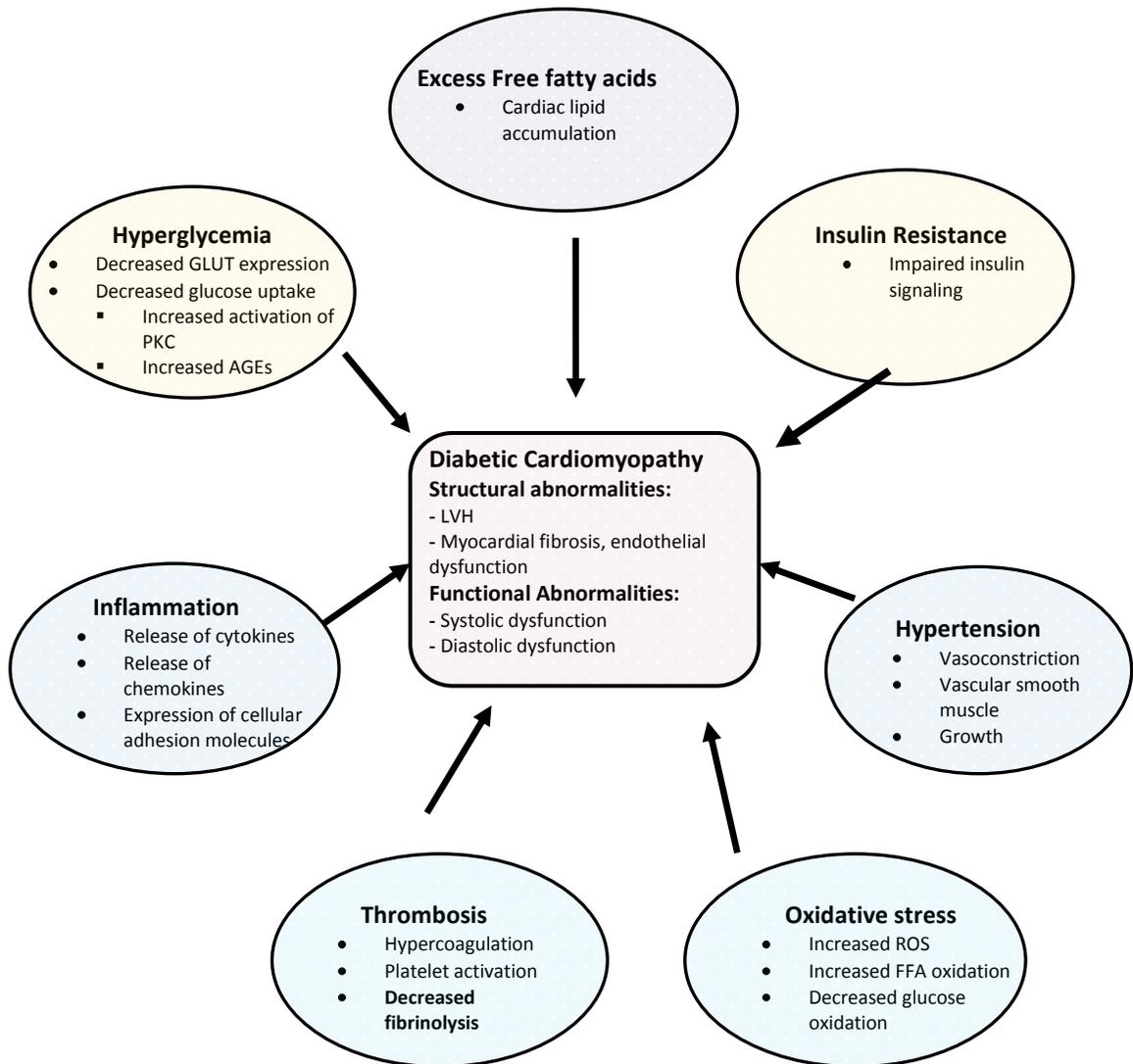


Figure 1: Pathophysiologic mechanisms in diabetic cardiomyopathy: in diabetes, hyperglycemia, excess free fatty acid (FFA) release, and insulin resistance, engender adverse metabolic events that affect the cardiac myocytes. Hyperglycemia is associated with decreased glucose transportation (GLUT), uptake, and oxidation, as well as increased formation of advanced glycation end products (AGEs) and increased activation of protein kinase C (PKC). Excess FFA release is followed by cardiac lipotoxicity, ie, increased cardiac lipid accumulation and increased generation of reduced reactive oxygen species (ROS) at the level of the electron transport chain. Together with insulin resistance and impaired insulin action and signaling, these metabolic paths augment vasoconstriction, produce and further aggravate arterial hypertension, increase inflammation with liberation of leukocyte-attracting chemokines, increase production of inflammatory cytokines, and augment expression of cellular adhesion molecules. Thrombosis is further promoted, together with platelet activation (*adapted from Voulgari et al. Diabetic cardiomyopathy: from the pathophysiology of the cardiac myocytes to current diagnosis and management strategies. Vasc Health Risk Manag.6:883-903*).

Figure 2: The Hypothetical link of metabolic alterations to LV function and coronary microcirculation in Diabetes Mellitus

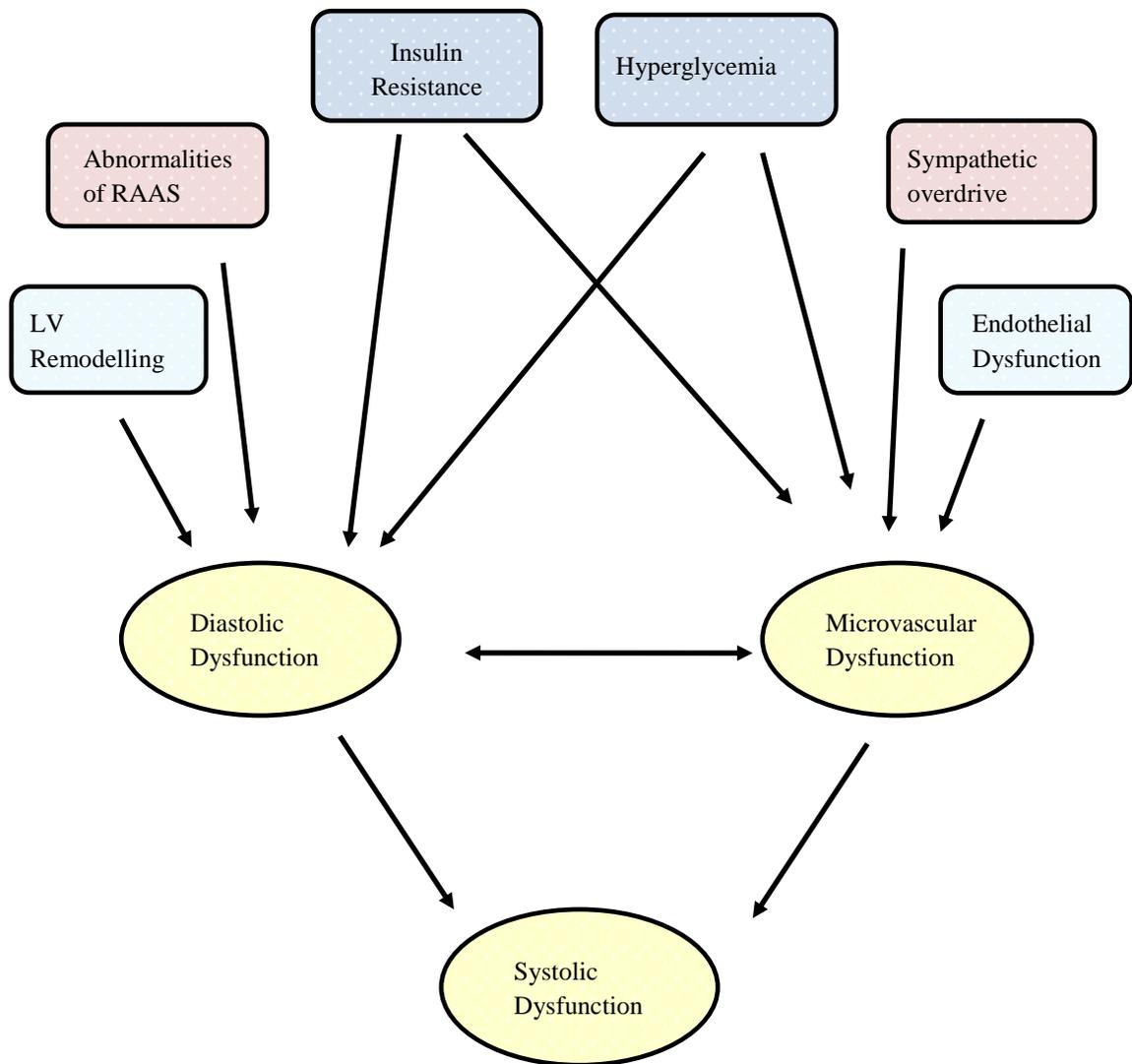


Figure 2: The hypothetical link of metabolic alterations to left ventricular (LV) function and coronary microcirculation in diabetes mellitus. Hyperglycemia, insulin resistance, sympathetic overdrive, endothelial dysfunction, abnormalities of the renin-angiotensin system (RAAS), and LV remodeling/hypertrophy may induce diastolic dysfunction (DD) and impairment of the coronary microcirculation. The microvascular alterations may induce DD or vice versa. The LV systolic involvement appears subsequent to DD and/or coronary microvascular dysfunction. (adapted from Galderisi M. Diastolic dysfunction and diabetic cardiomyopathy: evaluation by Doppler echocardiography. *J Am Coll Cardiol.* 2006 Oct 17;48(8):1548-51).

#### 4. Abnormalities of LV Function and Structure in Diabetic Cardiomyopathy.

Diabetic Cardiomyopathy (DCM) is characterised by structural abnormalities like Left ventricular hypertrophy (LVH) – related to adverse remodelling – systolic and diastolic dysfunction all of which can be diagnosed by a number of cardiac imaging techniques including echocardiography and Cardiac Magnetic Resonance Imaging (MRI) (12, 51).

Table 1 shows the main echocardiographic findings in population-based Studies on DCM.

Authors	Year	Echocardiographic Findings	Sample size (n)
Galderisi et al (61), Framingham Heart Study	1991	Increased LVM in women	111 DM; 381 IGT
Devereux et al (62), Strong Heart Study	2000	Increased LVM, reduction in ESF and MWSF	1810 DM
Palmieri et al (63), HyperGEN study	2001	Increased LVM and RWT, reduction of MWSF	386 DM + HTN
Ilercil et al (64), Strong Heart study	2001	Increased LVM and RWT	457 IGT
Bella et al (65), Strong Heart Study	2001	Progressive increase of LVM and reduction of ESF, MWSF in DM and DM+HTN	642 DM, 874 DM+HTN
Liu et al (66), Strong Heart study	2001	Progressive reduction in E/A ratio and prolongation of DT in DM and DM+HTN	616 DM, 671 DM+HTN
Rutter et al (67), Framingham Heart Study	2003	Progressive increase of LVM and RWT in IGT and DM	186 DM, 343 IGT

DM= diabetes mellitus; ESF= endocardial shortening fraction; HTN= hypertension; IGT= Impaired glucose tolerance; DT= deceleration time; LVM=left ventricular mass; MWSF= mid-wall shortening fraction; RWT= relative wall thickness.

##### 4.1 Increased LV Mass

The Framingham Study (68-70) as well as other population based studies (7, 71-73) have shown that increased left ventricular (LV) mass (or left ventricular hypertrophy), is an independent predictor of cardiovascular events in population-based studies using electrocardiograms or

echocardiography to define LVH. Left ventricular hypertrophy predicts cardiovascular disease in individuals without (68-70, 73) as well as with known coronary heart disease and heart failure (HF) (74, 75). Also, LV hypertrophy is now recognized as an independent indicator of diastolic dysfunction, irrespective of other supporting echocardiographic parameters, if the diagnosis is clinically suspected (76). Reduction of LV mass as a result of therapeutic intervention reduces cardiovascular events (77-80) indicating LV mass is an important subclinical marker of cardiovascular disease (81).

Geometric changes of the ventricle, termed remodeling, have been investigated primarily by echocardiography in relation to cardiovascular events (82-84). Echocardiographic estimates of LV hypertrophy [defined as LV mass index  $>122 \text{ g/m}^2$  in females and  $>149 \text{ g/m}^2$  in males according to the recent consensus of the European Society of Cardiology (76)] and the ratio of posterior wall thickness to LV radius  $\geq 0.45$  (84) have been used to define concentric remodeling of the left ventricle. The presence and pattern of ventricular remodeling has been noted to confer cardiovascular risk beyond LV hypertrophy in some studies (85-87) but not in others (88, 89). In the MESA cohort, Bluemke et al showed that LV mass had the strongest association with incident HF events (hazard ratio 1.4 per 10% increment,  $p < 0.0001$ ) and HF events occurred primarily in participants with LV hypertrophy, i.e.  $\geq 95$ th percentile of LV mass (HR 8.6, 95% CI, 3.7 – 19.9, reference group  $<50$ th percentile of LV mass) (90). On the other hand the endpoints of incident coronary heart disease and stroke were positively associated with increased LV mass to volume ratio (coronary heart disease, HR 2.1 per g/ml,  $p = 0.02$ ; stroke, HR 4.2 per g/ml,  $p = 0.005$ ). The greater risk conferred by LV hypertrophy in this study compared to other cohorts is due in part to the different methods of heart size assessment (MRI versus echocardiography or ECG) (90). The high accuracy and reproducibility of cardiac MRI (standard errors of about 5% (91-93) compared to 20% for echocardiography (94) in single center studies should facilitate risk estimates for short term studies that by nature will entail fewer events.

Another parameter related to LV mass is the LV volume to mass ratio which is also a feature of LV geometry. According to Corin et al, end-systolic volume/mass ratio describes LV geometry at the beginning of LV filling (95). Byrd et al suggested that LV volume/ mass was a better expression for the relation of LV volume to mass in determining wall stress, than LV mass/volume (96). The volume/mass ratio calculated from 2D echocardiography provides a precise, quantitative description of left ventricular geometry. Because end-systolic volume is highly dependent on the left ventricular contractile state, the end-diastolic volume/mass ratio is a more reliable measure of hypertrophy (96). When expressed quantitatively as a decrease in volume/mass ratio, concentric hypertrophy in patients with chronic pressure overload is easily understood - according to Laplace's law - as a response normalizing systolic wall stress (97).

Magnetic resonance imaging (MRI) is highly accurate and reproducible for assessing 3-dimensional (3D) ventricular size and shape (93, 98-101) and thus may allow additional insight into the pathophysiology of myocardial remodeling.

#### **4.2 Systolic Dysfunction**

The hallmark of systolic dysfunction is depressed LV ejection fraction ( $\text{End Diastolic Volume (EDV)} - \text{End Systolic Volume (ESV)} / \text{End Diastolic Volume}$ ) (12). Reduced ejection fraction (EF) has been established as a predictor of cardiovascular morbidity and mortality (17, 18) and is a predictor of incident HF, however it may not predict all HF as many with HF symptoms have “preserved” left ventricular (LV) EF(19, 20). Also, it may not be a good indicator of subclinical ventricular dysfunction in diabetes patients; in the MESA cohort, Bertoni et al found no significant difference in EF between diabetic and non-diabetic patients (16).

There are several echocardiographic techniques - principally taking into account systolic and diastolic volumes - which can help in the objective quantification of LV systolic function. Studies have shown that subtle systolic LV impairment may be missed on standard 2-dimensional

echocardiography, as visually the focus is on radial contraction and therefore early longitudinal dysfunction may be missed (102). Furthermore, in heart failure there is reduced long axis shortening which is compensated for by increased radial shortening.

Three dimensional tomographic techniques with adequate temporal and spatial resolution such as 3D-echocardiography, cardiac MRI and computed tomography provide more precise estimates of cardiac volumes and EF thus helping to describe LV function with better accuracy (103-105). Normal or mildly abnormal systolic LV function implies both an LVEF > 50% and an LV end-diastolic volume index (LVEDVI) < 97 ml/m<sup>2</sup> (76).

However, it is important to mention that ejection fraction has limitations imposed by load dependence and technical challenges, especially related to accurate tracing of endocardial borders and assumptions regarding LV geometry (106).

#### **4.3 Diastolic Dysfunction**

Up to 37% of individuals with diastolic heart failure have diabetes (107), and those with diabetes and diastolic heart failure have reduced survival (compared to non-diabetics) even after adjusting for covariates (108). Given that the prognosis in patients with established systolic dysfunction is poor, and deterioration is further accelerated by concomitant diabetes (109, 110) more attention has focused on establishing the importance of heart failure with preserved LV systolic function and determining criteria for diagnosing diastolic LV dysfunction, as these changes may be a precursor of systolic dysfunction. Diastolic dysfunction is believed to be the earliest functional change in diabetic cardiomyopathy and is closely correlated with glycated haemoglobin in diabetic patients (111).

Diastolic LV dysfunction is evident from slow LV relaxation and increased LV stiffness. Evidence of diastolic LV dysfunction requires objective evidence of abnormal relaxation, filling, diastolic distensibility and diastolic stiffness (76). In clinical practice this can be achieved through

cardiac catheterization, cardiac MRI or echocardiography (112). Due to its non-invasive and accessible nature, echocardiography has become a key diagnostic tool for establishing diastolic dysfunction via utilization of various recent techniques.

Doppler assessment of blood flow velocities was one of the first techniques employed to demonstrate evidence of diastolic dysfunction. Impaired LV relaxation, characterized by reduced early and increased late diastolic flow resulting in a characteristic inverse pulsed wave pattern (abnormal relaxation), is an early sign of diastolic dysfunction, grade I (12). More advanced grades, manifested by predominant early diastolic filling and rapid velocity deceleration (restrictive filling patterns), are associated with the most severe LV decompensation (113).

A more reliable method for estimating diastolic dysfunction is via tissue Doppler techniques which measure myocardial tissue velocity relative to a transducer (12). Early diastolic peak velocity (E') of the mitral annulus reflects the rate of myocardial relaxation and a reduction of annular E' was shown in recent-onset type 2 diabetes mellitus (114, 115).

Left atrial volume measurements and indices relative to body surface area have been shown to be strongly predictive of cardiovascular events and closely correlate with diastolic LV dysfunction (116). Therefore, a left atrial volume index  $>40$  ml/m<sup>2</sup> is considered to be sufficient echocardiographic evidence for diastolic dysfunction in the presence of non-conclusive tissue Doppler or when natriuretic peptides are elevated (76). In a population of 140 adults (16% diabetic), left atrial volume index was associated with the degree of diastolic dysfunction, independent of ejection fraction, age, gender, and cardiovascular risk score (116).

Cardiac MRI is increasingly recognized as a powerful diagnostic modality in cardiac disease and will likely emerge as an invaluable tool in detecting functional changes in the diabetic heart at an earlier stage than conventional investigations, as evidenced by a recent study combining cardiac

magnetic resonance spectroscopy and MRI to quantify myocardial triglyceride content in relation to decreased LV diastolic function in type-2-diabetic patients (117).

## **5. Myocardial Contraction Fraction (MCF) and Diabetic Cardiomyopathy.**

### **5.1 Rationale for the novel index – MCF.**

Assessment of ventricular function in patients with concentric hypertrophy is often challenging. Many patients with hypertrophy and heart failure may have “normal” or “preserved” left ventricular function as measured by conventional measures (118). In these patients, endocardial measures of ventricular function (shortening fraction [SF] or ejection fraction [EF]) may demonstrate normal or enhanced function (119, 120) while experimental (121-123) and clinical studies using a mid-wall measure of ventricular function (mid-wall shortening fraction [MWSF]) show depressed myocardial performance (124-126). Although three dimensional echocardiography yields highly accurate volumes and ejection fraction (EF) (127-129), a three-dimensional measure of myocardial shortening analogous to the two-dimensional MWSF had not been previously described. To address this, King et al describe a three-dimensional, volumetric measure of myocardial shortening, the myocardial contraction fraction (MCF), and compare it with two-dimensional echocardiographic measures of ventricular performance: the endocardial SF, the MWSF and the three-dimensional EF in normal subjects, patients with hypertensive hypertrophy and heart failure and subjects with physiologic hypertrophy.

Stroke volume (SV) is a measure of ventricular performance integrating the influence of all factors affecting the ventricle: preload, afterload, contractility and geometry. When it is assessed relative to end-diastolic pressure, fiber length or volume, or a related parameter, ventricular function is described (130). As a measure of myocardial shortening, SV is most appropriately assessed relative to the myocardium, and specifically to myocardial volume (MV), because it is the myocardium that shortens. Thus, myocardial contraction fraction defined as the ratio of stroke

volume to myocardial volume [ $MCF=SV/MV$ ], is a measure of ventricular function. In this ratio, SV is a measure of the amount by which the myocardium contracts (i.e., shortens) during systole relative to the total MV, although the myocardium itself has not undergone a reduction in volume (22). During systole the myocardium shortens and thickens, reducing its contained volume by the amount of the SV. Therefore, the SV is a measure of the amount of shortening and thickening that has occurred, and its ratio to MV could be seen as an index of the fractional shortening of the myocardium in volumetric terms.

Because this ratio removes the geometric influence of chamber volume (end-diastolic volume) from the denominator of the shortening expression, it was hypothesized that it may be a more useful measure of myocardial performance and could better delineate differences in ventricular function in patients with different degrees and types of hypertrophy than conventional measures.

To test this hypothesis, King et al compared the MCF obtained by freehand three-dimensional echocardiographic reconstruction of the LV with conventional two-dimensional echocardiographic measures of LV function in: 1) subjects with hypertensive hypertrophy, heart failure symptoms and preserved ejection fraction; 2) sedentary normal young to elderly adult male and female subjects; and 3) athletes with physiologic hypertrophy (21). The results showed that normal adults had a mean MCF of  $0.44\pm 0.07$ ; patients with hypertensive hypertrophy had lower values [ $0.33\pm 0.04$ ] while the athletes had higher values [ $0.55\pm 0.05$ ] ( $p<0.01$ ) reflecting a relatively greater increase in stroke volume than myocardial volume. The difference in endocardial shortening fraction between the normal subjects and athletes was not significant, whereas it was, as expected, significantly higher in the patients with hypertensive hypertrophy ( $p < 0.01$ ). Mid-wall shortening fraction (MWSF) was not significantly different among the three groups. Ejection fraction was normal in all three groups.

The primary finding of King's study was that MCF most clearly distinguishes the three groups whereas conventional shortening parameters—EF, endocardial SF and MWSF—do not (21). The endocardial SF was increased in concentric hypertrophy, due to geometric changes in the ventricle, but did not differentiate physiologic hypertrophy (in athletes) from sedentary normal subjects. In addition, MWSF did not distinguish between hypertensive and physiologic hypertrophy. Also, the lack of a statistically significant difference in MWSF across the groups may have been due to either variability of the two-dimensional measurement, small sample size, or the superimposition of clinical heart failure in the group with hypertensive hypertrophy. Thus, MCF which measures myocardial shortening in a manner qualitatively similar to the MWSF appeared to be more useful in comparing and differentiating physiologic hypertrophy from hypertensive hypertrophy than conventional measures. King et al suggested that the utility of MCF for more general application in other groups of patients should be considered (21).

Diabetic cardiomyopathy is characterised by LV hypertrophy and dysfunction so it is reasonable to think that MCF could better characterise the structural and functional abnormalities occurring in diabetic cardiomyopathy so we propose to use it in our study to test whether 1) it could be a better indicator of diabetic cardiomyopathy and 2) it predicts heart failure in a multi-ethnic cohort.

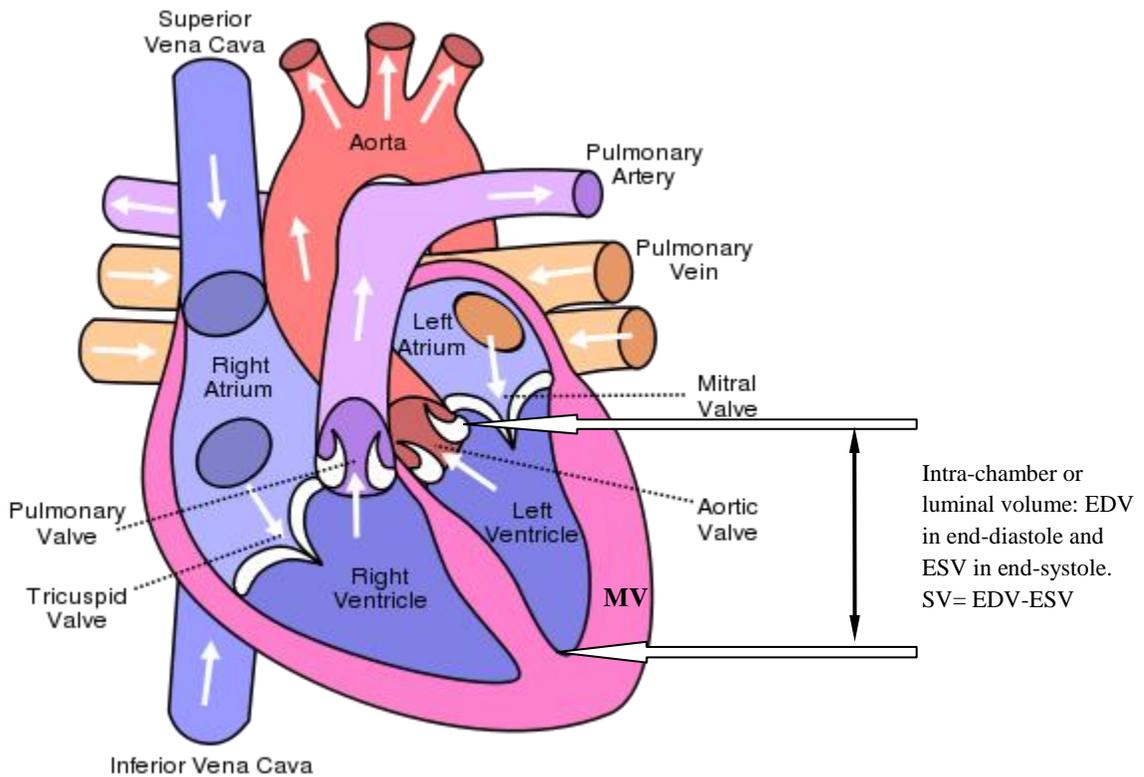
## **5.2 Major Features of MCF**

### **5.2.1 Influence of Chamber Volume**

Myocardial contraction fraction incorporates only SV in the numerator and MV in the denominator, thus removing the geometric influence of chamber volume and wall thickness from the denominator of the shortening expression. Each of the conventional indices of ventricular function—EF, SF and MWSF—incorporates the end-diastolic chamber dimension or volume in the denominator of its mathematical expression. In the case of the mid-wall shortening fraction (MWSF), the dimensions used are the sum of the ventricular dimension plus one-half the wall

dimension. As a consequence, assessment of shortening by these parameters is fully or partially influenced by chamber volume (end-diastolic chamber dimensions). By eliminating chamber volume from the denominator of the shortening assessment, the MCF expresses the shortening relationship only in terms of that which shortens the myocardium. It expresses left ventricular function per volume of myocardial fiber.

**Figure 3: Diagrammatic representation of MCF.**



**Figure 3:** Diagrammatic representation of the parameters involved in the shortening expression for myocardial contraction fraction. MV is myocardial volume. EDV is end-diastolic volume. ESV is end-systolic volume. SV is stroke volume.  $MCF = SV/MV$ . The denominator of MCF does not include the end-diastolic chamber dimensions.

### **5.2.2 Myocardial Shortening abnormality**

A decrease in MCF indicates abnormal myocardial shortening induced either by hypertrophy or by intrinsic myocardial disease that reduces SV. Geometric changes in hypertensive hypertrophy have been shown to mask a generalized myocardial shortening abnormality not apparent when endocardial measures of chamber function are employed (131). The MWSF studies have identified reduced function in some but not all hypertrophied subjects (125). The MWSF represents the contraction of the middle, circumferential layer of myocardial fibers at the base of the ventricle. It is not representative of all myocardial contraction because there is significant heterogeneity of myocardial fiber shortening not only from epicardium to endocardium, but also from apex to base. The MCF confirms the findings of studies using spatially modulated magnetic resonance imaging that show a generalized myocardial shortening abnormality with hypertrophy (132). The latter studies show depressed longitudinal as well as circumferential myocardial shortening in hypertensive hypertrophy (133).

### **5.2.3 MCF as measure of LV Function and LV Geometry**

Considering MCF mathematically,  $MCF = SV/MV$ . In this ratio, SV which is  $EDV - ESV$  is a measure of the amount by which the myocardium contracts during systole relative to the total MV. Therefore, the SV is a measure of the amount of shortening and thickening that has occurred, and its ratio to MV is an index of the fractional shortening of the myocardium in volumetric terms and thus a measure of LV function.

Furthermore, LVM is calculated by taking the difference of the end-diastolic endocardial and epicardial volume (obtained from summation of disks method from 11 cine short axis images) multiplied by 1.05 g/ml, which is the density of myocardium. Given that  $LVM = MV \times 1.05$ ,  $MV = LVM/1.05$ . We know that  $MCF = SV/MV$  and  $SV = EDV - ESV$  so MCF can also be expressed as  $1.05 \times [EDV/LVM - ESV/LVM]$ . Now, we know that  $EDV/LVM$  is the inverse of LV

concentricity in end-diastole and ESV/LVM is a similar parameter in end-systole. This suggests that apart from the quantity 1.05g/ml, MCF could be seen as a measure of LV geometry.

#### **5.2.4 Advantages of MCF.**

Myocardial contraction fraction has a clear, simple and easily understood definition. As a dimensionless index, analogous to the EF, it easily permits comparison of myocardial shortening between subjects. Also, it may be easily calculated by any three-dimensional tomographic technique, including MRI, computed tomography (CT) and 3D echocardiography. However, MCF requires accurate measurement of SV and MV, and its use may be restricted to three-dimensional techniques. Estimates of SV and MV obtained by two-dimensional techniques and Doppler echocardiography probably are neither sufficiently accurate nor reproducible to be comparable to three-dimensional results. Three-dimensional tomographic reconstruction of the ventricle, whether by echocardiography, MRI or CT, is the most accurate and reproducible method for obtaining chamber volume and MV at the present time (127). This accuracy and reproducibility are essential for the calculation of a useful MCF. Three-dimensional echocardiography and MRI have been shown to yield equivalent results that are superior to m-mode and two-dimensional echocardiographic techniques (103, 104, 134). The superior accuracy of three-dimensional tomographic reconstruction is based on several characteristics. First, three-dimensional methods avoid use of geometric assumptions by measuring an additional spatial dimension. Second, in free hand 3D echocardiography, visual guidance of image plane location decreases errors of image plane position. Third, three-dimensional methods decrease sampling errors by increasing about fivefold the number of images used to represent the ventricle (135).

However, MCF may not accurately reflect myocardial function where shortening (SV) is affected by valve disease. In the presence of regional disease, such as coronary artery disease, the MCF, as a global parameter, will reflect net myocardial shortening.

So, MCF is a useful measure for assessing myocardial shortening because it is independent of chamber size whereas conventional measures are not. As a volumetric measure of myocardial shortening, it parallels the two dimensional MWSF, confirming that myocardial shortening is decreased in hypertensive hypertrophy and increased in physiologic hypertrophy. Myocardial contraction fraction could also be useful in assessing myocardial function in patients with similar degrees of hypertrophy like diabetic patients.

## **SPECIFIC AIMS**

It is not known whether MCF differs by diabetes status or if it is predictive of heart failure in diabetic and non-diabetic persons. MESA will provide an opportunity to investigate these issues in a large multiethnic cohort.

We therefore aim to use the MESA cohort to: Investigate differences in MCF between subjects with normal fasting glucose (NFG), impaired fasting glucose (IFG) and diabetes and determine whether reduced MCF is predictive of incident HF.

We hypothesize that:

- 1- Myocardial contraction fraction is lower in subjects with IFG and diabetes compared to subjects with normal glucose. This association is present in whites as well as non-whites, and in both men and women, and is independent of age, hypertension, atherosclerosis, and endothelial dysfunction.
- 2- MCF is a significant independent predictor of incident HF.

## **METHODS**

### **1. Study Population:**

The Multi-Ethnic Study of Atherosclerosis (MESA) (136); specifically those who underwent baseline cardiac MRI and for whom diabetes status can be ascertained (4,991).

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study that began in July 2000 to investigate the characteristics of subclinical cardiovascular disease and risk factors that predict progression to clinically overt cardiovascular disease in a diverse, population-based sample of 6,814 men and women aged 45-84. MESA participants were recruited from 6 US communities (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; northern Manhattan, NY; and St. Paul, MN) and they were 38% Caucasian (n=2622), 28% African-American (n=1893), 22% Hispanic (n=1496), and 12% Chinese (n=803). Details regarding the design and objectives of MESA have been published (136). Individuals with a history of physician-diagnosed myocardial infarction, angina, heart failure, stroke, or transient ischemic attack, or who had undergone an invasive procedure for CVD (coronary artery bypass graft, angioplasty, valve replacement, pacemaker placement or other vascular surgeries) were excluded from the study at baseline.

### **2. Measures (exposures, outcomes and covariates).**

Data from the baseline exam and the events dataset will be used for these analyses. The major exposure of interest, diabetes, was defined based on use of anti-diabetic medication, and ADA criteria for fasting blood glucose (FBG $\geq$ 126 mg/dL). Impaired fasting glycemia was defined as: 100mg/dL<FBG $\leq$ 125mg/dL. The relevant covariates will be blood pressure/hypertension medication, age, gender; race, physical activity, smoking status, alcohol, urinary albumin/creatinine ratio, serum creatinine, and serum lipids (triglycerides, HDL and total

cholesterol), coronary artery calcium (CAC) and carotid intimal-medial thickness (IMT). The existing MRI data will be used to calculate MCF as  $[(SV/LVM) \times 1.05]$ .

The main outcome of interest will be incident heart failure. In MESA, HF cases were adjudicated by physician investigators and classified as definite, probable or absent. Definite or probable HF required heart failure symptoms, such as shortness of breath or edema, as asymptomatic disease is not a MESA endpoint. In addition to symptoms, probable HF required HF diagnosed by a physician and patient receiving medical treatment for HF. Definite HF required one or more criteria, such as pulmonary edema/congestion by chest X-ray; dilated ventricle or poor LV function by echocardiography or ventriculography; or evidence of left ventricular diastolic dysfunction. Participants not meeting any criteria, including just a physician diagnosis of HF without any other evidence, were considered as having no HF.

### **3. Power/sample size**

#### Aim1

Bertoni et al reported that among the 4,991 participants who underwent MRI and for whom glucose status could be ascertained, 26.7% ( $n = 1,334$ ) had IFG, 12.9% ( $n = 646$ ) had diabetes and the remaining 3011 had normal glucose (**16**). However we will use for the current paper the recalibrated glucose data. Thus we will use for our power calculations the following: 3834 normal glucose participants, 576 with IFG and 581 with diabetes. A preliminary analysis indicates the MCF mean is 0.65 with an SD of 0.14. Using a two-sample t-test (normal vs. IFG or DM) with a sample size of 3800 vs. 575, we have 89% power to detect a difference of 0.02 (that is, between 0.65 and 0.63). We have >99% power if the difference is greater than 0.04 (0.65 vs 0.61) (Calculated using SAS 9.2).

## Aim 2

MCF will be categorised into 4 quartiles and cox proportional hazards model will be used to calculate the hazard ratio for events (incident heart failure) comparing the lowest (Q1) to the highest quartile (Q4) of MCF.

In a Cox proportional hazards model, the null hypothesis can be tested using the score statistic which is the same as the log rank-test when we have 1 binary covariate. The power of the log-rank test depends on the number of deaths (events),  $d$  and is calculated using the Schoenfeld formula as:

$$d = \frac{4(Z_{1-\alpha/2} - Z_{1-\beta})^2}{[\ln HR]^2}$$

Where HR is the hazard ratio,  $Z_{1-\alpha/2}$  is the standard normal deviate at the 2-sided level of significance and  $Z_{1-\beta}$  is the power. Re-arranging this formula gives

$$Z_{1-\beta} = \frac{\sqrt{[d \times (\ln HR)^2]} - Z_{1-\alpha/2}}{4}$$

In the current MESA Events summary there are 149 cases of HF. Assuming that 70% of these had baseline MRI; that yields 104 cases of HF to investigate. Based on these findings we can calculate our power for  $\alpha=0.05$  as follows:

Number of events	Power		
	HR=1.50	HR=1.75	HR=2.0
104	54%	81%	94%

## **4. Statistical Analyses**

Aim 1: To investigate differences in MCF between subjects with NFG, IFG and diabetes

Unadjusted differences in MCF across the three glucose categories (normal, IFG, and diabetes) will be examined using ANOVA. If MCF is found to differ by sex and ethnicity in our initial analyses then the data will be investigated using sex and ethnicity-specific strata. We will do a comparison of the mean MCF of subjects with IFG and diabetes versus normal. Differences in MCF by glucose status will then be assessed using multivariable linear regression, with adjustment for all relevant covariates [blood pressure/hypertension medication, age, gender; race, physical activity, smoking status, alcohol, urinary albumin/creatinine ratio, serum creatinine, and serum lipids (triglycerides, HDL and total cholesterol), coronary artery calcium (CAC) and carotid intimal-medial thickness (IMT)].

Aim2: The prediction of incident heart failure by MCF will be investigated using cox proportional hazards models first with MCF as standardized continuous variables (Z-scores). Then MCF will be categorised into 4 quartiles and a Cox models will be used to investigate if the lowest quartile is associated with increased hazard for incident heart failure while controlling for potentially relevant covariates.

## **5. Human Subjects Protections**

### IRB Approval

The MESA study was approved by the Institutional Review Boards of each study site and written informed consent was obtained from all participants in accordance with guidelines for human experimentation of the US Department of Health and Human Services.

### Request for Exemption

Our current proposal will be a secondary data analysis of a de-identified dataset (MESA dataset) and so would not require contacting any study participants to collect new data or analysis of any stored samples.

Based on the requirements of exemption 4 of the DHHS regulations (46.101(b)) our proposal meets the criteria for exemption.

“Exemption 4: Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.”

#### Inclusion of Women, Children & Minorities

Women and minorities were included based on the targeted population as outlined in the MESA protocol (see [www.mesa-nhlbi.org](http://www.mesa-nhlbi.org)). MESA participants were recruited from 6 US communities and comprised 28% African-American (n=1893), 22% Hispanic (n=1496), and 12% Chinese (n=803). Women constitute almost 52.4% of those to be included in our analysis (4,991 participants who underwent MRI and for whom glucose status could be ascertained). MESA's primary hypotheses were concerned with the determinants and natural history of subclinical cardiovascular disease which takes decades to develop. Thus, children were not included in the study.

#### Data Management/Privacy and confidentiality

As a student (and lead author) working with an affiliated MESA investigator, the lead author has signed a data distribution agreement for affiliated investigators. Based on this premise the lead author agrees “not to attempt to personally identify any MESA participant based on the MESA data; not to attempt to contact any MESA participant; not to transfer or disclose any confidential data nor any information about individual MESA participants; not to except as necessary for data/safety monitoring or programmatic management, in the course of my responsibilities at work or in private, either during or after the conclusion of my affiliation with MESA; not to transfer any MESA data to individuals outside of the MESA group.”

Further, the lead author agrees to return all MESA data to the Coordinating Center or delete/destroy all electronic MESA data upon termination of his affiliation with the study and to notify the MESA Coordinating Center when he has done so.

**Myocardial contraction fraction, Diabetes and Heart Failure: The Multi-Ethnic Study of Atherosclerosis.**

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### **Structured Abstract**

**Objective:** We sought to investigate differences in myocardial contraction fraction (MCF) by glucose metabolism status and determine whether reduced MCF is predictive of incident heart failure (HF) in the Multi-Ethnic study of Atherosclerosis, a cohort study of 6814 adults aged 45-84 without prior cardiovascular (CV) disease.

**Background:** Diabetic individuals have altered cardiac structure and function which increases their risk for HF. Myocardial contraction fraction is an echocardiographic measure of fractional shortening recently applied to cardiovascular magnetic resonance (CMR).

**Methods:** We included 4991 participants who had CMR data for whom diabetes status could be ascertained. Left ventricular (LV) volumes and mass (LVM) were calculated by the summation of disks method from cine short axis images. MCF was calculated as LV stroke volume/LV myocardial volume. Diabetes (DM) and impaired fasting glucose (IFG) were defined according to the 2003 ADA established criteria. Linear regression was used to determine the potential association between MCF and diabetes status, after accounting for demographics and CV risk factors. Cox models were used to assess MCF, EF and LVM as predictors of HF adjusting for the above variables.

**Results:** MCF was lower in those with DM or IFG ( $p < 0.0001$ ) compared to subjects with normal fasting glucose (NFG). After full adjustment, those with IFG or DM exhibited a lower MCF [IFG -0.02 (95%CI -0.03, -0.01) DM -0.02 (95%CI -0.03, -0.001)] relative to those with NFG, while there was no significant difference in EF and LVM between glucose categories. Among diabetics 39.1% were in the 1<sup>st</sup> MCF quartile compared to 27% in the 1<sup>st</sup> EF quartile ( $p < 0.0001$ ). There were 96 cases of incident HF. Compared to the 4th quartile, the 1st MCF quartile was associated with HF [HR 2.1; 95%CI 1.0, 4.3] as was 1st EF quartile [HR 2.9; 95%CI 1.6, 5.3] and 4th quartile LVM [HR 4.9; 95%CI 1.9, 12.1].

**Conclusion:** After accounting for demographics and CV risk factors, MCF predicts future HF, and could better identify – than EF and LV mass – diabetic persons at risk for HF.

## INTRODUCTION

Heart Failure (HF) is a major and increasingly common cause of morbidity and mortality in the United States. (1-3). It has become a frequent manifestation of cardiovascular disease (CVD) among persons with type 2 diabetes mellitus (T2DM) (4, 5). As the prevalence of T2DM increases, it may emerge as one of the principal factors commonly associated with HF in the United States (6-8). Diabetic cardiomyopathy (DCM) is a distinct disease process partly responsible for the increased risk of HF in diabetic patients (12-15).

Bertoni et al have shown that ethnicity-specific differences in left ventricular mass, end-diastolic volume and stroke volume are associated with abnormal glucose metabolism and are independent of subclinical CVD in the MESA cohort (16); however no significant difference in ejection fraction (EF) by glucose metabolism category was found. Ejection fraction is a predictor of incident HF, however, reduced EF may not predict all HF cases as many HF patients have “preserved” left ventricular (LV) EF (19, 20). Using 3D echocardiography, a volumetric index, myocardial contraction fraction (MCF) defined as the ratio of left ventricular (LV) stroke volume (SV) to LV myocardial volume (MV) was used to discriminate between hypertensive patients with LV hypertrophy and athletes with physiologic hypertrophy (21). In the MCF parameter, SV is the amount by which the myocardium contracts (i.e., shortens) during systole relative to the total MV, although the myocardium itself has not undergone a reduction in volume. Because this ratio removes the geometric influence of chamber volume (end-diastolic volume) from the denominator of the shortening expression, it was hypothesized that it may be a more useful measure of myocardial performance and could better delineate differences in ventricular function in patients with different degrees and types of hypertrophy than conventional measures (21, 22).

We are unaware of the application of MCF to CMR, however the principles are the same, as volumes are calculated the same way in CMR and echocardiography (although with greater precision with CMR). Given that myocardial contraction fraction is an indicator of abnormalities in ventricular function and geometry (which are both characteristic of diabetic cardiomyopathy),

it may be useful for identifying those at risk for future HF related events. It is not known whether MCF differs between categories of glucose metabolism (Normal fasting glucose, impaired fasting glucose and T2DM) and the prognostic value of MCF regarding HF (or other cardiovascular events) in adults with and without abnormal glucose metabolism has also not been investigated.

These analyses use the MESA cohort to investigate differences in MCF between subjects with normal glucose, IFG and diabetes to determine if reduced MCF is predictive of incident HF.

## **METHODS**

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study that began in July 2000 to investigate the characteristics of subclinical cardiovascular disease and risk factors that predict progression to clinically overt cardiovascular disease in a diverse, population-based sample of 6,814 men and women aged 45-84. MESA participants were recruited from 6 US communities (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; northern Manhattan, NY; and St. Paul, MN) and were 38% Caucasian, 28% African-American, 22% Hispanic, and 12% Chinese. Details regarding the design and objectives of MESA have been published (136). Individuals with a history of physician-diagnosed myocardial infarction, angina, heart failure, stroke, or transient ischemic attack, or who had undergone an invasive procedure for CVD (coronary artery bypass graft, angioplasty, valve replacement, pacemaker placement or other vascular surgeries) were excluded from MESA; for these analyses we further excluded those without CMR or for whom diabetes status could not be determined.

Standardized medical history questionnaires and calibrated devices were used to obtain demographic data, tobacco usage, medical conditions, current prescription medication usage and anthropomorphic data. Fasting blood glucose and lipids were analyzed at a central laboratory. Serum glucose was measured by the Vitros analyzer (Johnson & Johnson Clinical Diagnostics). Diabetes was defined based on use of anti-diabetic medication; the ADA cut-offs for fasting blood glucose (FBG $\geq$ 126 mg/dL) and self-report. Impaired fasting glycemia was defined as:

100mg/dL < FBG ≤ 125mg/dL. Plasma lipids (HDL cholesterol and triglycerides) were measured after a 12 hour fast using a standardized kit (Roche Diagnostics). LDL cholesterol was calculated using the Friedewald equation (137). Resting seated blood pressure was measured three times using an automated oscillometric sphygmomanometer (Dinamap PRO 100; Critikon, Tampa, FL). The average of the last two measurements was used in analysis. Hypertension was defined as blood pressure ≥ 140/90 mmHg or current use of blood pressure medication. Body mass index (Kg/m<sup>2</sup>) was calculated from weight measured to the nearest 0.5Kg and height to the nearest 0.1cm

Chest computed tomography was performed using either a cardiac-gated electron-beam scanner or a prospectively electrocardiogram-triggered scan acquisition at 50% of the R-R interval with a multidetector system acquiring a block of four 2.5-mm slices for each cardiac cycle in a sequential or axial scan mode (136). Participants were scanned twice over phantoms of known physical calcium concentration. For each scan, a total phantom-adjusted Agatston score, defined as the sum of calcium measures from the left anterior descending, circumflex, and left and right coronary arteries, was calculated; the mean score was used in these analyses. Images of the right and left common carotid and internal carotid arteries were obtained using high-resolution B-mode ultrasound (138). For our analyses we used intima-media thickness (IMT) for the common carotid artery defined as the mean of all available maximum wall thicknesses across left and right sides and across left and far walls.

Cardiac magnetic resonance imaging (CMR) was performed using 1.5-Tesla magnets at each center; the MESA protocol has been described in detail (136, 139). Briefly, imaging was performed with a four-element, phased-array surface coil placed anteriorly and posteriorly, electrocardiogram gating, and brachial artery blood pressure monitoring. Cine images of the left ventricle were obtained during short breath-holding (12–15 s) at resting lung volume. Quantitative measurements were performed at one reading center using MASS (v4.2) analytical software for reader interpretation (Medis, Leiden, the Netherlands) by one of two trained

technicians. Left ventricular wall thickness was defined as the average of six midventricle segment thickness measurements. Left ventricular EDV and end-systolic volume (ESV) were calculated by summing the areas on each separate slice multiplied by the sum of the slice thickness. End-diastolic myocardial volume was determined by the sum of the area between the epicardial and endocardial contours multiplied by the slice thickness; this value was then multiplied by the specific gravity of myocardium (1.05 g/ml) to obtain the end-diastolic LVM. Ejection fraction was calculated as stroke volume divided by EDV. The inter-reader intraclass correlation coefficients were 0.98 for LVM and EDV, 0.94 for ESV and stroke volume, and 0.81 for ejection fraction. The intrareader coefficients for these measures ranged from 0.94 to 0.98. Myocardial contraction fraction was defined as  $SV/MV$  which is equivalent to  $[(SV/LVM) \times 1.05g/ml]$ .

#### *Adjudication of events*

Participants were followed for incident HF events for up to 6.4 yrs (median follow-up time). In addition to the 3 follow-up exams, a telephone interviewer contacted each participant at intervals of 9-12 months to inquire about all interim hospital admissions, cardiovascular outpatient diagnoses and procedures, and deaths. In order to verify self-reported diagnoses, copies of all death certificates and medical records for all hospitalizations and selected outpatient cardiovascular diagnoses and procedures were requested. Next of kin interviews for out of hospital cardiovascular deaths were obtained. Hospital records were obtained on an estimated 98% of hospitalized cardiovascular events and information on 95% of outpatient diagnostic encounters. Trained personnel abstracted any hospital records suggesting possible cardiovascular events. They recorded symptoms, history and biomarkers; scanned ECGs, echocardiograms, catheterization reports, outpatient records, and other relevant diagnostic and procedure reports. Potential end points were adjudicated by physician investigators who reviewed relevant medical records.

Reviewers classified HF as definite, probable, or absent. Definite or probable HF required heart failure symptoms, such as shortness of breath or edema, as asymptomatic disease is not a MESA endpoint. In addition to symptoms, probable HF required HF diagnosed by a physician and patient receiving medical treatment for HF. Definite HF required one or more criteria, such as pulmonary edema/congestion by chest X-ray; dilated ventricle or poor LV function by echocardiography or ventriculography; or evidence of left ventricular diastolic dysfunction. Participants not meeting any criteria, including only a physician diagnosis of HF without any other evidence, were considered not to have HF.

### *Statistical Analysis*

Unadjusted differences in baseline characteristics between the three glucose categories were investigated using One-way ANOVA for continuous variables and Chi square ( $\chi^2$ ) for categorical variables. Univariate differences in MCF and Tests for trend across glucose categories were carried out. Bertoni et al found differential effects of glucose status on LV mass and volumes by ethnicity and sex (16), so we tested (multiple partial F-tests) for glucose status-ethnicity and glucose status-sex interactions in the relationship between glucose status and MCF as well as glucose status and EF. Using multivariable linear regression, we investigated differences in MCF (and EF) across glucose categories with adjustment for age, sex, ethnicity and clinic site (model 1). We found significant glucose status by sex interaction in models for EF but not for MCF. Also, we found no significant glucose status by ethnicity interaction in models for EF or MCF. Thus subsequent analyses were carried out in sex strata adjusting for ethnicity. Subsequent models incorporated smoking status (current vs never and former vs never), systolic blood pressure, total and HDL cholesterol, body mass index, alcohol consumption (current vs never and former vs never), physical activity (model 2) and coronary calcium (CAC) and carotid IMT (model 3) to determine whether adjustment for these potential confounders altered the relationship between glucose category and myocardial contraction fraction. We defined CAC as

present or absent using the Agatston score. These analyses (ANOVA and multivariable linear regression) were repeated for ejection fraction.

The prediction of incident heart failure by MCF or EF was investigated using separate cox proportional hazards models in which MCF or EF were standardized continuous variables (Z-scores) or categorical variables (quartiles). Unadjusted cox proportional models were calculated for incident heart failure using MCF Z-score in order to obtain standardized regression coefficients. In multivariable models, age; gender; clinic site; ethnicity (model 1); smoking status; systolic blood pressure; glucose status; total and HDL cholesterol; body mass index; alcohol consumption; physical activity (model 2); CAC and carotid IMT (model 3) were incorporated to determine whether adjustment for these potential confounders altered the relationship between myocardial contraction fraction and incident heart failure. Subsequent analyses were performed with glucose status (diabetics vs non-diabetics) as a stratifying variable rather than a covariate. Similar models were fit using MCF quartiles in place of MCF Z-score.

These analyses (univariate and multivariable Cox models) were repeated using EF Z-score and subsequently, EF quartiles as the main predictor. Two-tailed P-values < 0.05 were considered significant. Analyses were performed using SAS Enterprise Guide 4.3 (SAS Institute Inc).

## **RESULTS**

Of the 6814 adults recruited by MESA, 5004 had CMR data and diabetes status could not be ascertained in 13 participants leaving a sample of 4991. Among the participants included, the proportion with diabetes was 11.6% (n=581) while those with IFG were 12.9% (n=645).

Compared to those excluded from the analyses (n=1823), the sample included was younger (61.5 vs 63.8yrs), more likely to be Caucasian (38.5 vs 36.8%) and male (47.6 vs 45.9%), less likely to have diabetes (15.5% among those excluded), and had lower body mass index (27.7 vs 30.0Kg/m<sup>2</sup>). As seen on Table II, there was a significant difference in racial composition between the glucose categories with a greater proportion of minorities having diabetes

( $p < 0.0001$ ). Age, weight, BMI, systolic blood pressure all increased significantly across glucose categories.

*Differences in MCF, EF and LV mass across Glucose categories*

The mean MCF was  $0.65 \pm 0.14$ . The MCF variable was normally distributed with a 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup> and 95<sup>th</sup> percentile of 0.55, 0.64, 0.74 and 0.90 respectively. MCF was higher in whites ( $p < 0.0001$ ) compared to other race/ethnic groups; was higher in men ( $p < 0.0001$ ) and has a significant negative correlation with age ( $r = -0.14$ ,  $p < 0.0001$ ). The distribution of LV parameters by glucose status is presented in Table II. In unadjusted models MCF was significantly lower in those with abnormal glucose metabolism (IFG  $-0.05$ ; DM  $-0.07$ ,  $p < 0.0001$ ) compared to participants with normal fasting glucose. There was no significant difference in EF between the three glycemic groups ( $p = 0.1$ ). Also, there was a significant trend of decreasing mean MCF from normal ( $0.66 \pm 0.14$ ) to IFG ( $0.61 \pm 0.14$ ) to diabetes ( $0.59 \pm 0.14$ ) ( $p < 0.0001$ ). Conversely, there was no significant trend in either direction for mean EF between diabetes subjects ( $68.5 \pm 8.5$ ) and subjects with IFG ( $69.1 \pm 7.9$ ) and normal glucose ( $69.1 \pm 7.1$ ) ( $p = 0.11$ ) (Table II).

Across the three glycemic groups there was a significant trend of decreasing LV mass ( $p < 0.0001$ ) and a marginally significant trend for SV ( $p = 0.047$ ).

Furthermore, among diabetics, 39.1% were in the 1<sup>st</sup> MCF quartile compared to 27.2% in the 1<sup>st</sup> EF quartile and 33% in the 4<sup>th</sup> LVM quartile ( $p < 0.0001$ ); this proportion decreased for the 2<sup>nd</sup> to the 4<sup>th</sup> MCF quartiles ( $p < 0.0001$ ) while there was no significant difference for quartiles of EF ( $p = 0.07$ ) (Table III).

Table IV shows differences in MCF, EF and LV mass between normal and IFG or diabetes in multivariable models. Individuals with diabetes and impaired fasting glucose had a significantly lower MCF than subjects with normal fasting glucose (NFG) after adjustment for demographics and clinic site (model 1). These differences were attenuated but remained significant after adjustment for cardiovascular risk factors (model 2) and subclinical atherosclerosis (model 3). On the other hand, for both EF and LV mass there was no significant

difference between IFG and NFG or Diabetes and NFG after full adjustment for demographics, CV risk factors, renal function and subclinical atherosclerosis.

We found evidence of a significant differential relationship of glucose status to ejection fraction by sex interaction ( $p < 0.005$ ) with no evidence of glucose status-sex interaction observed in models for MCF. The stratified analyses showed a similar pattern with lower MCF in diabetics (vs normal) in both men and women but there was no significant difference in MCF between IFG and normal in women (data not shown). Also, diabetic men had a significantly lower EF than men with normal glucose but this difference wasn't observed between IFG and normal glucose.

#### *Prediction of incident heart failure by MCF, EF and LV mass*

There were 96 cases of incident HF reported during the 6.5 median years of follow-up. Compared to participants with no HF, participants who developed HF were older (68.8 vs 61.4yrs); were more likely to be male (63.5 vs 47.3%), diabetic (29.2 vs 11.3%), hypertensive (73.4 vs 41.8%) and had higher median albumin-creatinine ratio (9.5 vs 5.2 mg/g). The results of unadjusted and multivariable Cox proportional hazards models for incident HF events with MCF and EF as standardized variables (Z-scores) are shown on Table V. In univariate analysis, higher MCF was significantly associated with a decreased risk for incident HF (HR, 0.41 per SD increase in MCF,  $p < 0.0001$ ). In a separate unadjusted model, higher EF was equally associated with a decreased risk in incident HF but the hazard ratio (HR, 0.55 per SD increase in MCF,  $p < 0.0001$ ) was higher. After adjustment for demographics (model 1), CV risk factors (model 2) and subclinical atherosclerosis (model 3) and in separate models, MCF and EF remained negatively associated with incident heart failure (Table V) and these patterns were similar for both diabetic and non-diabetic subjects. On the other hand, higher LV mass was significantly associated with an increased risk for incident HF in both univariate (HR, 2.09 per SD increase in LV mass,  $p < 0.0001$ ) and multivariable models (Table V).

Results were similar for separate models based on MCF, EF and LV mass quartiles. In the unadjusted models, the HR for participants in the 1<sup>st</sup> quartile versus those in the 4<sup>th</sup> quartile of

MCF was 5.20 [2.8-9.7] ( $p < 0.0001$ ) (Table VI). The HR for participants in the 1<sup>st</sup> quartile versus those in the 4<sup>th</sup> quartile of EF was 2.6 [1.6-4.5] ( $p < 0.0001$ ) (Table VI). In multivariable models, the HR of quartile 1 vs quartile 4 for MCF decreased as we adjusted for demographics then CV risk factors and subclinical atherosclerosis while the HR for EF remains relatively unchanged. The hazard ratios for quartiles 2 and 3 vs quartile 4 for both EF and MCF were not significantly different from 1. For LV mass, the unadjusted HR for participants in the 4<sup>th</sup> quartile versus those in the 1<sup>st</sup> quartile was 6.5 [3.2-13.1] ( $p < 0.0001$ ) (Table VI) and this value equally decreased after full adjustment.

## DISCUSSION

In this diverse, cohort of individuals that were free of cardiovascular disease at baseline we had two main findings. Myocardial contraction fraction was significantly lower among participants with DM and impaired fasting glucose compared to those with normal fasting glucose independently of demographics, cardiovascular risk factors, renal function and subclinical atherosclerosis. This trend did not exist for EF and LV mass. Secondly, an increase in MCF was associated with a significantly reduced risk of incident HF independently of demographics, CV risk factors and subclinical atherosclerosis and this relationship was similar in diabetic as well as non-diabetic participants.

Diabetic cardiomyopathy is characterized essentially by a latent subclinical period, during which cellular structural insults lead initially to left ventricular hypertrophy and diastolic dysfunction and eventually systolic dysfunction (**12**), the hallmark of which is depressed LV ejection fraction (**12**). In the current study we found no significant differences in EF and LV mass between glucose categories (IFG and NFG or Diabetes and NFG) in multivariable analyses except for lower mean EF in men with IFG vs NFG in stratified analyses. Conversely, we found a significant trend of decreasing MCF across glucose categories and among diabetics the proportion of individuals in the 1<sup>st</sup> MCF quartile was greater than in the 1<sup>st</sup> EF quartile. These findings

suggest that among diabetics, MCF may be able to better identify persons at risk for HF, than EF and LV mass. A plausible explanation for this could be that MCF is a hybrid measure of an LV function index (stroke volume) and a structural measure (LV mass); the incipient stages of diabetic cardiomyopathy being characterized by structural abnormalities while the later stages involve overt changes in myocardial performance.

Furthermore, MCF expresses the myocardial shortening in a more intuitive fashion, as SV/MV, and as such, that takes away the geometric influence of chamber volume (21). Myocardial contraction fraction (which is a dimensionless index as is EF makes it easy to compare myocardial shortening between subjects) could thus be seen as a measure of myocardial performance per volume of myocardial fiber. Therefore, in diabetic individuals, a decrease in MCF would indicate abnormal shortening induced by hypertrophy and myocardial fibrosis secondary to the pathophysiologic consequences of hyperglycemia, insulin resistance and other metabolic derangements (51, 140).

Also, the fact that MCF is significantly higher in persons with impaired fasting glucose suggests that myocardial shortening is compromised early-on even before overt diabetes ensues. Therefore, persons with IFG may be at increased risk for HF. This is corroborated by the fact that previous studies have linked impaired glucose tolerance to endothelial dysfunction (141-144) and left ventricular hypertrophy (64, 67) both of which are precursors of impaired myocardial performance (54, 56).

The results of the current study also showed that MCF – as well as EF and LV mass – is a significant independent predictor of incident HF events. The relationship between MCF and incident HF may be explained in part by the fact that previous studies have established increased LV mass (the denominator for the MCF parameter) as a feature of diastolic dysfunction found in diabetic cardiomyopathy and overt heart failure (12, 76). However, after adjustment for demographics and traditional CV risk factors the predictive ability of MCF decreased. Such a trend wasn't apparent for EF. This suggests that the risk conferred by MCF was confounded in

part by CV risk factors including older age; albuminuria and diabetes – diabetes status was independently associated with MCF (but not EF) and is a known risk factor for HF. This confounding could be explained by the fact that previous studies have demonstrated a relationship between these CV risk factors (older age, microalbuminuria and diabetes) and increased LV mass **(62, 145-148)**.

The strengths of our study include: the use of a well-described, large, multi-ethnic population-based sample; the greater precision provided by using cardiac CMR to calculate MCF which was previously described using 3D echocardiography **(21)** and using the most recent ADA cut-offs for glucose categories. However there are a couple of weaknesses which need to be underscored. The generalizability of the results is limited by selection and survivor biases. Given that MESA recruited only subjects free of cardiovascular disease at baseline, the older individuals included in the studied sample were a relatively healthy subset of the general population.

In conclusion, in this cohort of adults free of cardiovascular disease at baseline, MCF (an index for myocardial shortening) could better identify diabetic persons at-risk of HF, than EF and it is a significant independent predictor of heart failure. This relationship maybe mediated in part by traditional CV risk factors. In future studies, it would be interesting to compare the 95<sup>th</sup> percentile of MCF and EF against a gold standard definition of diabetic cardiomyopathy using receiver operating curve (ROC) analyses. This would permit us to better understand the role of MCF as an indicator of diabetic cardiomyopathy and define cut-points for persons at risk of future heart failure.

Furthermore, using a cohort with a larger sample of diabetic subjects would permit more robust inferences but also the study of subgroups like those with additional comorbidities like hypertension. Further investigation will be required to study the relationship between MCF, clinical parameters (like HbA1c and diabetes duration) in type 2 diabetes and heart failure. Furthermore, it may be interesting to investigate the effect of ACE inhibitors and lifestyle

measures (weight loss and increased physical fitness) on myocardial contraction fraction (as a surrogate endpoint) in persons with type 2 diabetes in a clinical trial setting.

At present time there are no clear strategies for prevention of HF among persons with DM. Future studies (including trials) may wish to identify diabetic persons at highest risk of HF; MCF may have advantages over EF and LV mass for doing so.

Table II: Baseline characteristics of MESA participants with CMR data by glucose metabolism status, 2000-2002.

Characteristic	NFG	IFG	Diabetes	P-value
n	3765	645	581	
Age (yrs)	60.7±10.1	64.0±9.8	64.4±9.2	<0.0001
Female (%)	54.8	43.6	46.8	<0.0001
Weight (Kg)	75.6±15.9	81.3±16.1	81.6±16.6	<0.0001
Height (cm)	166.5±9.9	166.5±9.8	165.7±10.2	0.24
BMI (Kg/m <sup>2</sup> )	27.2±4.8	29.2±5.0	29.6±5.2	<0.0001
Race				<0.0001
White (%)	43.5	31.1	19.3	
Chinese-American (%)	12.1	17.1	13.9	
African-American (%)	23.9	25.9	36.8	
Hispanic (%)	20.5	25.3	30.0	
Total Cholesterol (mmol/l)	195.3±34.9	194.3±35.4	188.2±37.8	<0.0001
LDL Cholesterol (mmol/l)	118.0±31.0	117.7±30.5	111.4±33.3	<0.0001
HDL Cholesterol (mmol/l)	52.71±15.3	46.8±12.7	46.3±12.9	<0.0001
CAC present (%)	44.9	56.6	63.9	<0.0001
Agatston Score	110.6±339.4	175.2±436.2	252.4±58.5	<0.0001
IMT (cm)	0.84±0.18	0.89±0.19	0.94±0.20	<0.0001
Hypertension (%)	36.7	54.6	65.6	<0.0001
BP Medication (%)	29.4	45.2	65.6	<0.0001
Systolic BP (mmHg)	123.3±20.7	131.7±21.5	132.1±22.1	<0.0001
Diastolic BP (mmHg)	71.4±10.2	74.2±10.7	71.8±10.2	<0.0001
Serum Creatinine (mg/dl)	0.95±0.2	0.97±0.2	0.98±0.6	<0.0001
ACR (mg/g)	4.7±5.2	6.6±9.7	11.6±26.2	<0.0001
Smoking				
Current Smokers	12.81	12.31	12.41	0.92
Former Smokers	35.4	37.8	36.9	0.40
Alcohol Use (%)				
Current alcohol use	59.2	54.7	39.2	<0.0001
Former alcohol use	21.3	24.2	33.8	<0.0001
Total Moderate and Vigorous activities (MET-min/wk)	4221.3±5535.0	3765.0±5287.5	3528.8±5985.0	0.0002
MCF	0.66±0.14	0.61±0.14	0.59±0.14	<0.0001
EF (%)	69.1±7.1	69.2±7.9	68.5±8.5	0.11
SV(ml)	86.7±20.1	85.7±19.0	85.9±19.0	0.047
LVM (g)	142.2±38.1	152.6±41.4	157.4±42.6	<0.0001

Data are presented as mean±SD or proportions. P-values are for trends across glucose categories.

Table III: MCF and EF quartiles for Diabetics in the MESA cohort, 2000-2002.

	MCF Quartiles				Total	P-value
Diabetes	Q1	Q2	Q3	Q4		
Frequency (n)	227	153	115	86	581	
Percentage (%)	39.1	26.3	19.8	14.8	100	<0.0001
	EF Quartiles					
Diabetes	Q1	Q2	Q3	Q4		
Frequency (n)	158	150	120	153	581	
Percentage (%)	27.2	25.8	20.7	26.3	100	0.07

Data presented are proportions of persons in MCF and EF quartiles among diabetics. P-values are for chi-square tests.

Table IV: Differences in MCF, EF and LV mass between IFG or diabetes and normal in multivariable models among MESA participants

	IFG		Diabetes	
	$\beta$ coefficient (95% CI)	P-value	$\beta$ coefficient (95%CI)	P-value
<b>MCF</b>				
Model 1	-0.03(-0.04, -0.02)	<0.0001	-0.04 -0.05, -0.03)	<0.0001
Model 2	-0.01(-0.02, -0.005)	0.004	-0.02 (-0.03, -0.008)	0.0007
Model 3	-0.02 (-0.03, -0.006)	0.002	-0.02 (-0.03, -0.0007)	0.002
<b>EF</b>				
Model 1	0.14 (-0.44, 0.71)	0.63	-0.57 (-1.18, -0.03)	0.06
Model 2	0.08 (-0.50, 0.67)	0.78	-0.61 (-1.27, 0.04)	0.07
Model 3	0.07 (-0.52, 0.67)	0.81	-0.64 (-1.30, 0.01)	0.06
<b>LVM</b>				
Model 1	7.83 (5.29, 10.37)	<0.0001	11.57 (8.83, 14.25)	<0.0001
Model 2	-1.00 (-3.27, 1.30)	0.40	-0.33 (-2.86, 2.20)	0.80
Model 3	-0.59 (-2.87, -1.68)	0.61	-1.40 (-3.93, 1.12)	0.27

Parameter estimates in table are differences ( $\beta$  coefficients) between normal and IFG or diabetes. Model 1 is adjusted for age, gender, race, clinic site. Model 2 is Model 1 plus BMI, hypertension, BP medication, total cholesterol, HDL cholesterol, serum creatinine, Log urinary albumin-creatinine ratio, smoking status, alcohol, and physical activity. Model 3 is Model 2 plus CAC category and carotid IMT.

Table V: Hazard ratio of incident HF associated with a 1 SD increase in MCF and EF in univariate and multivariable models.

	HR	95%CI	P-value
<b>MCF</b>			
Unadjusted	0.41	(0.33, 0.51)	<0.0001
Model 1	0.49	(0.39, 0.62)	<0.0001
Model 2	0.59	(0.46, 0.76)	<0.0001
Model 3	0.59	(0.45, 0.75)	<0.0001
<b>EF</b>			
Unadjusted	0.55	(0.48, 0.63)	<0.0001
Model 1	0.55	(0.48, 0.64)	<0.0001
Model 2	0.58	(0.50, 0.68)	<0.0001
Model 3	0.57	(0.50, 0.68)	<0.0001

<b>LVM</b>			
Unadjusted	2.09	(1.85, 2.38)	<0.0001
Model 1	2.30	(1.97, 2.69)	<0.0001
Model 2	2.09	(1.72, 2.54)	<0.0001
Model 3	2.10	(1.73, 2.54)	<0.0001

Table VI: Hazard ratio of Incident HF for MCF, EF and LV mass quartiles in univariate and multivariable models.

	<b>MCF</b>		<b>EF</b>		<b>LVM</b>	
	<b>HR (95% CI)</b>	<b>P-value</b>	<b>HR (95% CI)</b>	<b>P-value</b>	<b>HR (95% CI)</b>	<b>P-value</b>
<b>Unadjusted</b>						
Q1	5.19 (2.78, 9.65)	<0.0001	2.62 (1.57, 4.51)	0.0005	Referent	
Q2	1.52 (0.73, 3.17)	0.26	1.17 (0.63, 2.20)	0.63	1.78 (0.79, 4.05)	0.2
Q3	0.63 (0.28, 1.65)	0.39	0.61 (0.29, 1.29)	0.20	1.70 (0.75, 3.90)	0.2
Q4	Referent		Referent		6.48 (3.21, 13.10)	<0.0001
<b>Model 1</b>						
Q1	3.08 (1.57, 6.08)	0.001	2.66 (1.47, 4.80)	0.001	Referent	
Q2	1.14 (0.54, 2.40)	0.74	1.26 (0.66, 2.41)	0.48	2.0 (0.84, 4.51)	0.1
Q3	0.56 (0.23, 1.38)	0.21	0.67 (0.31, 1.42)	0.39	2.0 (0.84, 4.85)	0.1
Q4	Referent		Referent		8.36 (3.63, 19.24)	<0.0001
<b>Model 2</b>						
Q1	2.09 (1.01, 4.31)	0.046	2.87 (1.56, 5.38)	0.0007	Referent	
Q2	0.94 (0.43, 2.05)	0.88	1.47 (0.76, 2.84)	0.25	1.56 (0.67, 3.66)	0.3
Q3	0.50 (0.20, 1.26)	0.14	0.70 (0.39, 1.53)	0.38	1.50 (0.60, 3.73)	0.4
Q4	Referent		Referent		4.70 (1.88, 11.64)	<0.001
<b>Model 3</b>						
Q1	2.08 (1.01, 4.30)	0.047	2.89 (1.57, 5.33)	0.0007	Referent	
Q2	0.94 (0.43, 2.05)	0.87	1.46 (0.75, 2.84)	0.26	1.58 (0.68, 3.70)	0.3
Q3	0.49 (0.20, 1.24)	0.13	0.71 (0.37, 1.52)	0.37	1.52 (0.61, 3.78)	0.4
Q4	Referent		Referent		4.85 (1.94, 12.13)	<0.001

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## CHAPTER THREE

There were two main findings in this study: 1) Myocardial contraction fraction (MCF) was significantly lower among diabetic subjects and subjects with impaired fasting glucose compared to those with normal glucose independently of demographics, CV risk factors and subclinical atherosclerosis. Such a trend did not exist for ejection fraction (EF). 2) An increase in myocardial contraction fraction significantly reduces the risk of incident heart failure events independently of demographics, CV risk factors and subclinical atherosclerosis and this relationship is similar in diabetic as well as non-diabetic subjects.

In this chapter we added ancillary analyses not included in the manuscript intended for submission to *The Journal of the American College of Cardiology* and future directions for this line of research. Trend tests for diabetes proportions across MCF and EF quartiles are presented including stratified (by gender) linear models differences in MCF and EF across glucose categories. Best-fit prediction models for MCF based on demographics, CV risk factors and measures of subclinical atherosclerosis are also presented. Plots of cumulative hazard for MCF and EF quartiles and stratified (by gender) cox models for the prediction of incident HF are also included in this section.

### 1. Ancillary Analyses

#### 1.1 Diabetes Prevalence in MCF and EF Quartiles

The prevalence of diabetes in the 1<sup>st</sup> quartile of MCF was significantly greater than in the other quartiles [18.2 vs 12.3, 9.2, 6.9;  $p < 0.0001$ ] and there was a significant trend of increasing diabetes proportions across the MCF quartiles ( $p < 0.0001$ ) while no such trend was observed across quartiles of EF ( $p = 0.35$ ).

Table VII: Proportion of diabetics in quartiles of MCF and EF in the MESA cohort, 2000-2002.

	MCF Quartiles				P-value
Diabetes (n=581)	Q1 (n=1248)	Q2(n=1248)	Q3(n=1248)	Q4(n=1247)	
Frequency (n)	227	153	115	86	
Percentage (%)	18.2	12.3	9.2	6.9	<0.0001
	EF Quartiles				
Diabetes (n=581)	Q1(n=1248)	Q2(n=1248)	Q3(n=1248)	Q4(n=1248)	
Frequency (n)	158	150	120	153	
Percentage (%)	12.7	12.1	9.6	12.3	0.35

Values in the table are number of diabetics and corresponding percentages per quartile of EF and MCF. P-values are for trend across quartiles.

### 1.2 Box and Whisker Plots for Differences in MCF and EF across Glucose categories

Figure 4: Differences in MCF across categories of Glucose metabolism

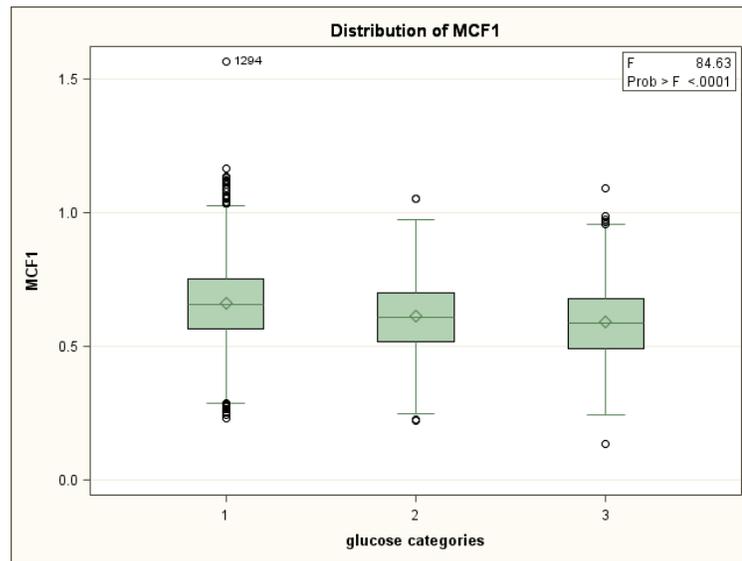
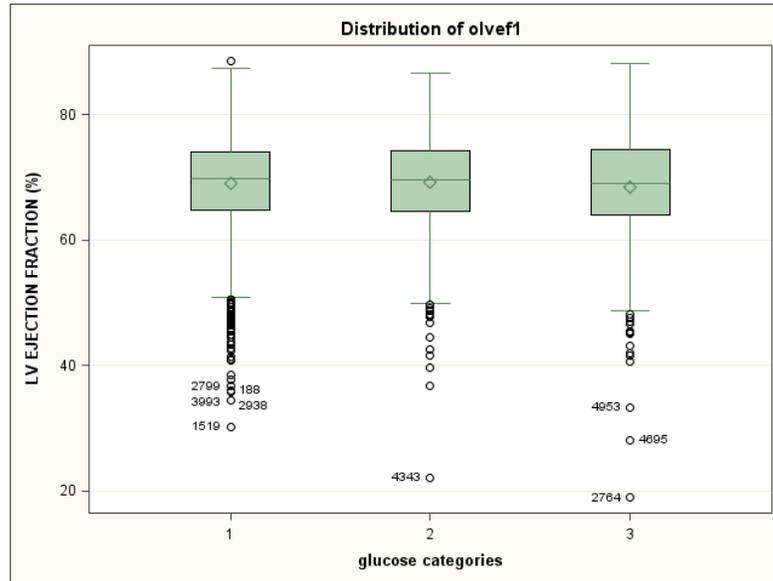


Figure 5: Differences in EF across categories of glucose metabolism.



### 1.3 Differences in MCF and EF across Glucose categories By Gender

Stratified models showed lower MCF in impaired fasting glucose and diabetics in both males and females but this relationship wasn't apparent in females with IFG after full adjustment. For ejection fraction, as in the unstratified analysis, there was no significant difference between normal fasting glucose and IFG or diabetes in females. However, diabetic males had a significantly lower EF than males with normal glucose even after full adjustment. This difference wasn't observed between IFG and normal glucose.

Table VIII: Differences in MCF and EF between IFG or diabetes and normal after multivariable linear regression among MESA participants stratified by gender

	<b>Males</b>				<b>Females</b>			
	IFG		Diabetes		IFG		Diabetes	
	Coef (95% CI)	P-value	Coef (95% CI)	P-value	Coef (95% CI)	P-value	Coef (95% CI)	P-value
<b>MCF</b>								
Model 1	-0.03 (-0.05, -0.02)	0.0004	-0.04(-0.06, -0.03)	<0.0001	-0.03(-0.05, -0.01)	0.0004	-0.05 (-0.07, -0.03)	<0.0001
Model 2	-0.02 (-0.03, -0.005)	0.008	-0.02 -0.03, -0.004)	0.045	-0.01 (-0.02, 0.007)	0.27	-0.02 (-0.04, -0.01)	0.004
Model 3	-0.02 (-0.03, -0.006)	0.004	-0.01(-0.03, -0.002)	0.09	-0.01 (-0.02, 0.006)	0.25	-0.02 (-0.04, -0.01)	0.006
<b>EF</b>								
Model 1	-0.3 (-1.1, 0.5)	0.50	-1.5 (-2.4, -0.6)	0.001	0.6 (-0.2, 1.3)	0.12	0.3 (-0.5, 1.1)	0.41
Model 2	-0.3 (-1.1, 0.5)	0.51	-1.3 (-2.3, -0.3)	0.007	0.5 (-0.3, 1.3)	0.23	0.2 (-0.7, 1.0)	0.69
Model 3	-0.4 (-1.2, 0.4)	0.36	-1.3 (-2.2, -0.3)	0.01	0.6 (-0.2, 1.5)	0.13	0.1 (-0.7, 1.0)	0.78

Parameter estimates in table are differences ( $\beta$  coefficients) between normal and IFG or diabetes. Model 1 is adjusted for age, gender, race, clinic site Model 2 is Model 1 plus BMI, hypertension, BP medication, total cholesterol, HDL cholesterol, serum creatinine, Log urinary albumin-creatinine ratio, smoking status, alcohol, and physical activity. Model 3 is Model 2 plus CAC category and carotid IMT.

#### 1.4 Prediction of MCF.

A backward elimination procedure was used for selecting a best-fit model for predicting MCF from a maximum model comprising demographics (age, gender and ethnicity), CV risk factors (diabetes status, systolic blood pressure and BP drugs, BMI, smoking status, serum lipids, physical activity, microalbuminuria), renal function, history of alcohol use and measures of subclinical atherosclerosis (CAC and carotid IMT). The objective was to have an idea of which subset of variables were most important in predicting MCF. The significance level to leave the model was set at 0.10. Analyses were carried out for the entire cohort (with diabetes status as a covariate) then in diabetes strata.

Table IX: Variables included in the best-fit prediction model

<b>Variable</b>	<b>Regression Coefficient</b>	<b>Standard Error</b>	<b>P-value</b>
Intercept	0.94	0.021	<0.0001
Age	-0.0005	0.0002	0.02
Gender	-0.01	0.004	<0.0001
BMI	-0.002	0.0004	<0.0001
SBP	-0.001	0.0001	<0.0001
HDL cholesterol	0.001	0.0001	<0.0001
DM	-0.02	0.006	0.001
IFG	-0.02	0.005	0.003
LOG ACR	-0.01	0.002	<0.0001
Chinese	0.035	0.006	<0.0001
African American	-0.04	0.004	<0.0001
Current smoking	-0.04	0.005	<0.0001
Former alcohol use	-0.01	0.004	0.01
Carotid IMT	-0.06	0.01	<0.0001
Coronary calcium	-0.016	0.004	<0.0001

Age, gender, BMI, systolic blood pressure, HDL cholesterol, diabetes status (diabetes and impaired fasting glucose vs normal), log albumin-creatinine ratio (ACR), ethnicity (chinese and African American), current smoking status, former alcohol use, carotid intima media thickness and coronary calcium were retained in the best-fit prediction model. A similar prediction model was obtained in stratified (by diabetes status) analysis:

Table X: Variables included in Prediction model for Diabetics

Variable	Regression coefficient	Standard Error	P-value
Intercept	0.96	0.02	<0.0001
Age	-0.0006	0.0002	0.015
Gender	-0.10	0.004	<0.0001
BMI	-0.002	0.0004	<0.0001
SBP	-0.0008	0.0001	<0.0001
HDL cholesterol	0.0006	0.0001	<0.0001
LOG ACR	-0.01	0.002	<0.0001
Chinese	0.03	0.006	<0.0001
African American	-0.04	0.005	<0.0001
Current smoking	-0.05	0.006	<0.0001
Former alcohol use	-0.01	0.005	0.01
Carotid IMT	-0.06	0.01	<0.0001
Coronary calcium	-0.02	0.004	0.0002

**1.5 Hazard Ratios for Incident HF per SD increase in MCF and EF stratified by Diabetes Status.**

Table XI: Hazard ratio for incident HF associated with 1SD increase in MCF and EF in univariate and multivariable models stratified by diabetes status.

	HR	95%CI	P-value
<b>Diabetics (n= 585)</b>			
Unadjusted	0.50	(0.34, 0.75)	<0.0001
Model 1	0.50	(0.32, 0.78)	<0.0001
Model 2	0.56	(0.34, 0.92)	<0.0001
Model 3	0.57	(0.34, 0.97)	<0.0001
<b>Non-diabetics (n=4410)</b>			
Unadjusted	0.41	(0.32, 0.54)	<0.0001
Model 1	0.52	(0.40, 0.70)	<0.0001
Model 2	0.60	(0.49, 0.82)	<0.0001
Model 3	0.59	(0.44, 0.80)	<0.0001

### 1.6 Plots of Hazard Function for MCF and EF Quartiles.

The plots of hazard function (in figures 5 and 6) show a greater hazard for quartile 1 vs quartile 4 of MCF and EF with a more than 5 fold increased risk for heart failure for quartile 1 of MCF and more than 2 fold increased risk of HF for quartile 1 of EF.

Figure 6: Cumulative hazard for incident heart failure by quartiles of MCF

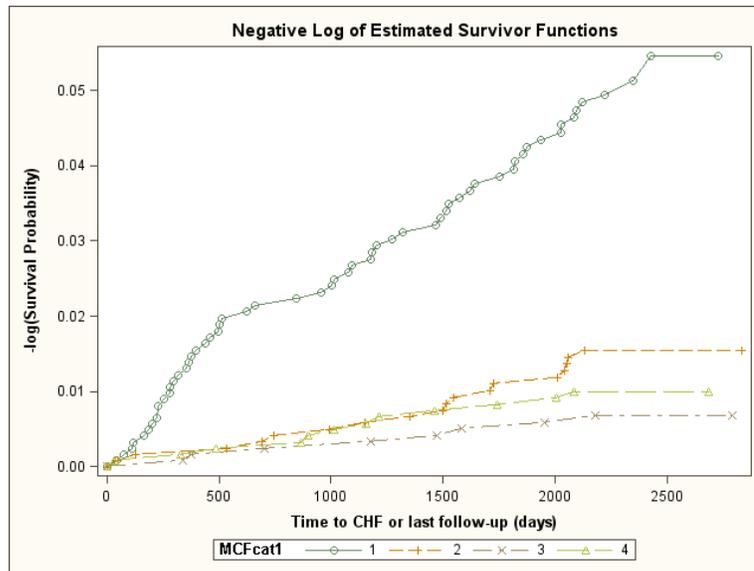
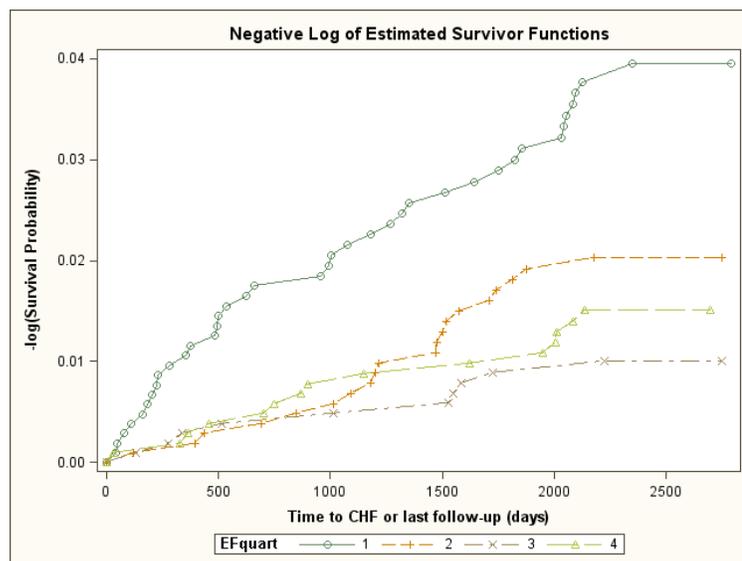


Figure 7: Cumulative hazard for incident heart failure by quartiles of EF



## **2. Conclusions and future Directions**

The study was focused on investigating myocardial contraction fraction (compared to EF) as an indicator of abnormal LV function in persons with dysglycemia and as a predictor of incident heart failure. Based on our findings we have been able to show that it may be a better indicator – than EF – of myocardial performance in persons with impaired glucose metabolism given its hybrid nature (incorporating a measure of function and structure).

In future studies, it would be interesting to compare the 95<sup>th</sup> percentile of MCF and EF against a gold standard definition of diabetic cardiomyopathy using receiver operating curve (ROC) analyses. This would permit us to better understand the role of MCF as an indicator of diabetic cardiomyopathy and define cut-points for persons at risk of future heart failure.

Furthermore, using a cohort with a larger sample of diabetic subjects would permit more robust inferences but also the study of subgroups like those with additional comorbidities like hypertension. Further investigation will be required to study the relationship between MCF, clinical parameters (like HbA1c and diabetes duration) in type 2 diabetes and heart failure. Furthermore, it may be interesting to investigate the effect of ACE inhibitors and lifestyle measures (weight loss and increased physical fitness) on myocardial contraction fraction (as a surrogate endpoint) in persons with type 2 diabetes in a clinical trial setting.

At present time there are no clear strategies for prevention of HF among persons with DM.

Future studies (including trials) may wish to identify diabetic persons at highest risk of HF; MCF may have advantages over EF and LV mass for doing so.

## CURRICULUM VITAE

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### EDUCATION

**2009 – 2012:** Masters program in Clinical and Population Translational Science at Wake Forest University.

**1999 – 2006:** Doctor of Medicine degree obtained at The Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Cameroon.

**1997 – 1999:** General Certificate of Education (GCE) Advanced Level at Baptist High School, Buea, Cameroon

### COMPLEMENTARY COURSES

- Training course on The Management of diabetes and related comorbidities and complications in 3 major medical centers in Paris, France: Saint Louis, Robert Debré and La Pitié Salpêtrière. The course was coordinated by the Endocrine and Diabetes Unit of The Saint Louis Hospital in Paris (**March 2007**).

- Training course on Diabetes Epidemiology in Stellenbosch, South Africa organised by the International Diabetes Epidemiology Group (**IDEG, November 2006**).

- Training workshop on Diabetes education organised by The Pan-African Diabetes Educators Group (**March 2008**).

- Good Clinical Practice (GCP) and Research Methods Course organized by the Effective Care Research Unit (ECRU), University of Fort Hare, East London (**June 2009**).

- Training course on the Data Analysis using SPSS 15.0 for windows organised by faculty from The University of Newcastle upon Tyne (**March 2006**).
- Training workshop on Project management organised by the Cameroon Burden of Diabetes office in partnership with the German Cooperation (**May 2006**).
- Research Methods Course in Sexual & Reproductive Health and HIV in Johannesburg, organized by the Reproductive Health and HIV Research Unit of the University of Witwatersrand and sponsored by the World Health Organisation, Geneva and the HIV Research Trust, UK (**August 2009**).

## **PROFESSIONAL APPOINTMENTS AND ACTIVITIES**

### **Department of Epidemiology and Prevention, Wake Forest University Health Sciences.**

- Research assistant for Dr Alain Bertoni, working on 2 projects: determinants of Brain Natriuretic Peptide in Diabetes, an ancillary study to LOOK AHEAD and Prediction of Incident Diabetes in a Multi-Ethnic Population, an ancillary study to The Multi-Ethnic Study of Atherosclerosis (MESA). (**February 2010-now**)

### **Department of Endocrinology and Metabolism, National Obesity Center, Yaoundé Central Hospital, Cameroon (2006- 2007).**

- Attending physician caring for patients with Diabetes and related comorbidities.
- Organising seminars on the primary prevention and management of diabetes in collaboration with faculty, The Ministry of public health and Pharmaceutical companies.
- Served as the main speaker during several seminars organized by pharmaceutical companies on dyslipidemia and the relevance of lipid lowering therapy in Sub-Saharan Africa.

### **District Hospital Kumba, Cameroon (2008-2009)**

- Consulting physician for HAART-related metabolic complications and coordinator of the HIV treatment Unit.
- Certified ECG and Ultrasound technician.
- Chair of Morbidity and Mortality committee.

## **INTERNATIONAL CONFERENCES AND SEMINARS**

- 10th Symposium of the International Diabetes Epidemiology Group, Stellenbosch, South Africa, **November 2006**.

- 19th World Diabetes Congress, Cape Town International Convention Centre, Cape Town, South Africa, **December 2006**. I presented 3 abstracts as posters.

- Annual Congress of the French Diabetes and Metabolic Disease Association (ALFEDIAM/SFE joint congress), Marseille, France, **March 2007**. I was co-author of 1 abstract.

- European Type 1 Diabetes Genetics Network (ET1DGN) 6th Annual Meeting, Barcelona, April 2007. I was awarded a prize for the best trio pilot.

## **RESEARCH EXPERIENCE**

**2008 - 2009:** Research assistant for the Cameroon Diabetes Epidemiology Registry project in collaboration with the Vrije University in Brussels and the Gestational Diabetes project funded by the Wellcome Trust.

**2006 - 2008:** Co – investigator at the Cameroon site for the Type 1 Diabetes Genetics Consortium; an international, multicenter program organized to promote research to identify genes and their alleles that determine an individual's risk for Type 1 diabetes.

**2006 - 2007:** Co-investigator at the Endocrine and Diabetes Center for the multicenter study on the determinants of diabetic foot ulcers in collaboration with the Manchester Royal Infirmary.

**2006 - 2007:** Research assistant at the Cameroon site for the International HbA1c Standardisation Study, a multicenter project organised by the ADA/EASD/IDF working group and the Cameroon burden of Diabetes Project sponsored by The World Diabetes Foundation.

**2005 - 2006:** Conducted 3 cross-sectional studies on diabetes complications the results of which were presented at the World Diabetes Congress in 2006.

## **PUBLICATIONS**

### **Presented as posters during the 19th world diabetes congress:**

**E Akwo**, Ndip A, V Effoe, G Ashuntantang, E Sobngwi and J Mbanya. Relationship between diabetic kidney disease and other microvascular complications of diabetes in Cameroonian type 2 diabetic patients (abstract). *Diabetic medicine*, 23 (suppl. 4), 1-199, Dec 2006.

**E Akwo**, J Nwatsock, G Ashuntantang, A Ndip, V Effoe, E Sobngwi and J Mbanya. Prevalence and Clinical significance of dyslipidaemias in a population of Sub Saharan type 2 diabetic patients (abstract). *Diabetic medicine*, 23 (suppl. 4) 1-199, Dec 2006.

**E Akwo**, A Ndip, V Effoe, B Nouthé, E Sonbgwi and J Mbanya. Semiquantitative measurement of plantar pressure: footprints obtained at points-of-care using diluted betadine™ solution (abstract). *Diabetic medicine*, 23 (suppl. 4) 411-607, Dec 2006.

**Presented as a poster during the ALFEDIAM/SFE Joint Congress:**

S. P. Choukem, **E. Akwo**, M. Raphael, P. Vexiau, J. C. Mbanya, E. Sobngwi and J. F. Gautier. Clinical profile and prevalence of microvascular complications in type 2 diabetic patients of African decent living in France compared to those living in Cameroon. *Diabetes and Metabolism-Annales d'Endocrinologie*. March 2007.

**Article submitted to the Editor, Diabetic Medicine:**

S. P. Choukem, **E. Akwo**, L. S. Fetita, F. F. J. Kaze, P. Vexiau, J. C. Mbanya, E. Sobngwi and J. F. Gautier. Migration from Sub-Saharan Africa to France is associated with earlier development of type 2 diabetes (under review).

**Article published in Diabetic medicine in 2009:**

E Sobngwi, AL Lekoubou, MY Dehayem, BE Nouthe, EV Balti, F Nwatsock, **EA Akwo**, VS Effoe, VT Balla, AS Mamdjokam, V Siaha, CA Tabi, A Mvom, I Djam, JC Mbanya. Evaluation of a simple management protocol for hyperglycaemic crises using intramuscular insulin in a resource-limited setting. *Diabetes and Metabolism*, 35 (2009) 404-409.

**CURRENT RESEARCH**

Alain G. Bertoni, **Elvis A. Akwo**, Gregory Burke, David Bluemke, Joao A. Lima, Gregory W. Hundley, Haiying Chen, Songtao Liu. Myocardial contraction Fraction, Diabetes and Heart Failure: The Multiethnic Study of Atherosclerosis. (Masters' thesis, manuscript intended for submission to the *Journal of the American College of Cardiology*).

**PROFESSIONAL INTERESTS:**

Research interests:

- Epidemiology and prevention of the cardiovascular complications of diabetes mellitus.

- Molecular mechanisms and genetic basis of type 2 diabetes and atherosclerosis.

Clinical interests:

- Internal Medicine/Cardiology

### **INVITED PRESENTATIONS**

- Guest speaker during a talk on the public health impact of surgical and chronic conditions at the Wake Forest University Reynolda campus.
- Presented a poster on diabetic dyslipidemia during the graduate school research day 2009 at Wake Forest University.

### **MEMBERSHIP IN PROFESSIONAL ORGANIZATIONS**

- Member of the Cameroon National Medical Council (CNMC).
- Member of the Pan-African Diabetes Educators Group (PADEG).

### **HONORS AND AWARDS**

- Tuition Scholarship (\$30,658) awarded by the Wake Forest University Graduate School for the Masters' program in Clinical and Population Translational Sciences (**2009-2012**).
- Best trio pilot for the Type 1 Diabetes Genetics Consortium Project (**Barcelona, 2007**).
- World Health Organization (WHO) Scholarship to attend RHRU Research Methods Course at The South African College of medicine in Johannesburg (**August 2009**).
- Wellcome Trust Scholarship to attend Research Methods Course at Effective care Research Unit, University of Fort Hare, East London (**June 2009**).
- Young Investigator Grant from the International Diabetes Federation to attend the World Diabetes Congress in Cape Town, South Africa (**December 2006**).
- New Investigator Scholarship from the International Diabetes Epidemiology Group (IDEG) to attend the IDEG Diabetes Epidemiology training course (**November 2006**).
- INSERM (National Institute of Health and Medical research) Bursary to attend French Diabetes Congress and complementary training on Diabetes Management at The Saint Louis Hospital, Paris (**March 2007**).

- Junior Chamber International, Cameroon Annual Awards: Most promising young physician (2009).

### **VOLUNTEERING AND COMMUNITY SERVICE**

- Performed free screening for diabetes and high blood pressure during activities of the World Diabetes Day (2006-2008).

- As a member of the Pan African Diabetes Educator's Group (PADEG) and a physician, I led biannual trainings of nursing staff on the early diagnosis and management of diabetic emergencies in rural health clinics and primary care settings twice a year (2006-2009).

- Volunteered in the activities of the World Kidney Day: screening for Chronic Kidney Disease, sensitizing communities on the burden and risk factors for Chronic Kidney Disease and the importance of dialysis and organ donation.

- Performing free screening for HIV in rural communities during the activities of the World AIDS Day in partnership with with Junior Chamber International (JCI), Cameroon (2005-2008).

- Training of peer educators for HIV sensitization in rural communities.

- Performing radio and TV interviews for the Roll-back Malaria program.

- Volunteered in the nation-wide Mosquito nets distribution project.

### **FACULTY ADVISOR**

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