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## Research Article

# Long-term survival of patients with ischemic cardiomyopathy and diabetes as compared to those without diabetes undergoing myocardial viability assessment with $^{18}\text{F}$ FDG-PET

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## ABSTRACT

**Objective:**  $^{18}\text{F}$ FDG-PET is considered the most sensitive test to detect hibernating myocardium. We compare the predictive value of  $^{18}\text{F}$ FDG-PET for long-term survival of patients with ischemic cardiomyopathy and diabetes versus those without diabetes that were referred for  $^{18}\text{F}$ FDG-PET to assess hibernating myocardium. **Patients and methods:** 80 patients (24 diabetics) with angiographically documented ischemic cardiomyopathy who underwent myocardial perfusion scintigraphy with  $^{99\text{m}}\text{Tc}$ -tetrofosmin and myocardial viability evaluation by  $^{18}\text{F}$ FDG PET/CT (after hyperinsulinemic-euglycemic clamp protocol with acipimox) were investigated. Median follow-up after viability testing was  $62.4 \pm 33.2$  months.

**Results:** All patients had impaired left ventricular ejection fraction (mean  $32.9 \pm 9.3\%$ ). Diabetic patients had fewer percent of scar tissue ( $16.0 \pm 12.0$ ) as compared to nondiabetic patients ( $25.7 \pm 18.7$ ) ( $p < 0.01$ ), while the amount of hypoperfused and viable myocardium was not significantly different ( $14.5 \pm 12.6$  vs.  $9.8 \pm 12.0$ ) ( $p = 0.21$ ). 12 patients had 1 vessel disease (VD), 15 patients 2 VD, 49 patients 3 VD, and 4 patients diffuse calcification in stenotic coronary arteries. Diabetic patients had significantly more commonly 3 VD than nondiabetic patients (83% vs. 52%,  $p < 0.01$ ). The number of revascularization procedures in diabetic patients and nondiabetic patients was statistically not significantly different (71% vs. 54%,  $p = 0.55$ ). Median survival was 69.3 months (60.1-77.9 months) in nondiabetic patients and 46.5 months (32.7-60.3 months) in diabetic patients ( $p < 0.001$ ).

**Conclusions:** Patients with ischemic cardiomyopathy, impaired LVEF and diabetes exhibited significantly reduced overall survival compared to those without diabetes though having less scarred and equal amounts of viable myocardium as indicated by  $^{18}\text{F}$ FDG-PET.

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## Introduction

Coronary artery disease (CAD) complicated by severe impaired left ventricular function is associated with high morbidity and mortality.

Coronary revascularization may lead to symptomatic and prognostic improvement in such patients [1,2]. However, prospective identification of patients with ischemic cardiomyopathy and heart failure who may

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benefit from high risk revascularization remains a clinical challenge [1-3]. Hibernating myocardium, i.e., chronically hypoperfused myocardium leading to a hypocontractile state, is likely to benefit from revascularization as opposed to scarred myocardium. Reperfusion is known to potentially reverse wall motion abnormalities and improve left ventricular function of viable myocardium [1, 3]. Therefore, myocardial viability assessment is increasingly being used to identify CAD patients who are most likely to benefit from coronary revascularization procedures.

To detect the presence of viable myocardium, stress echocardiography, single-photon-emission computed tomography (SPECT) [1, 3] and more recently  $^{18}\text{F}$ -fluorodesoxyglucose (FDG)-positron emission tomography (PET) have been used. Recently data from a study in 601 patients did not confirm the prognostic value of viability assessment by SPECT or stress echocardiography for survival or efficacy of coronary revascularization [1].  $^{18}\text{F}$ FDG-PET has been shown to have the highest sensitivity to detect hibernating myocardium [3,4], and CAD patients were found to benefit from PET-assisted management [5, 6].  $^{18}\text{F}$ FDG-PET seems to define high-risk patients that gain benefit from coronary revascularization. However, little agreement exists about the amount of viable myocardium needed to achieve a relevant improvement of left ventricular ejection fraction (LVEF) of  $> 5\%$ . Proposed cut-off-points range from 7% to 37% of left ventricular area [7].

Diabetic patients have increased mortality and morbidity from cardiovascular diseases, independent of other risk factors [8-10]. Revascularization procedures are associated with a higher morbidity and mortality in patients with diabetes mellitus than in nondiabetic patients [11].

In this study, we investigate retrospectively the long-term survival of patients with ischemic cardiomyopathy, impaired LVEF and diabetes as compared to those without diabetes that were referred for myocardial viability assessment with  $^{18}\text{F}$ FDG-PET.

## Methods

A cohort of eighty consecutive patients (71 males and 9 females, mean age of  $71.3 \pm 9.8$  years) with predominantly symptoms of heart failure that had angiographically documented ischemic cardiomyopathy, fixed perfusion defects in  $^{99\text{m}}\text{Tc}$ -tetrofosmin SPECT, impaired LVEF and were referred for  $^{18}\text{F}$ FDG-PET for viability assessment to detect hibernating myocardium at our Institution between 2011 and 2015 were included in this study. Patients with deaths attributed to non-cardiac causes were excluded from this investigation. Fifty-four patients had previous acute myocardial infarction.

All patients underwent myocardial perfusion scintigraphy using  $^{99\text{m}}\text{Tc}$ -tetrofosmin and evaluation of myocardial viability by  $^{18}\text{F}$ FDG-PET/CT using a combination of hyperinsulinemic-euglycemic clamp protocol with acipimox. Inclusion criteria for  $^{18}\text{F}$ FDG-PET imaging were wall motion abnormalities in previous clinical echocardiographic evaluation, fixed perfusion defects in  $^{99\text{m}}\text{Tc}$ -tetrofosmin SPECT and LVEF  $< 50\%$ .

Median time of follow-up (performed with conventional protocols for cardiac patients) was  $62.4 \pm 33.2$  months after viability testing.

All patients signed an informed consent. The study was in accordance with the declaration of Helsinki and approved by an institutional review board.

Myocardial perfusion was assessed with  $^{99\text{m}}\text{Tc}$ -tetrofosmin (4 MBq/kg body weight) gated SPECT using a two-day stress/rest protocol and pharmacologic stress with adenosine (140  $\mu\text{g}/\text{kg}$  body weight/minute for 4 minutes). Acquisition (rotation  $90^\circ$ , 34 s/projection,  $64 \times 64$  matrix) was done using a Siemens E.CAM gamma camera with a low-energy high-resolution-collimator. Quantitative myocardial perfusion analysis was performed on a 17-segment model using 4 DM-SPECT software.

Metabolic activity was measured with  $^{18}\text{F}$ FDG-PET (4.2 MBq/kg body weight), following a euglycemic-hyperinsulinemic protocol (250 mg acipimox at least one hour before tracer injection). A Siemens Biograph 6 PET-Scanner,  $168 \times 168$  matrix, iterative reconstruction and 5 mm FWHM filter were used.

Myocardial viability assessment was based on the concept of perfusion-metabolism mismatch found in myocardium with previously determined contractile dysfunction. Mismatch was expressed as a percentage of the left ventricle.

Revascularization was intended in our Institution when the amount of hypoperfused but viable myocardium exceeded 10% of left ventricular area. However, we included also in this study 13 patients with coronary artery stenosis and myocardial viability  $< 10\%$  that have been revascularized at other institutions, and 3 other patients with myocardial viability  $> 20\%$  that have refused revascularization in our Institution.

## Statistical analysis

Data consistencies were checked, and data were screened for outliers and normality using quantitative plots. Potential confounders were adjusted for survival analysis. Two-sided, independent t-tests with and without the assumption of variance homogeneity were used to compare various variables between both groups. The association between overall survival and diabetes was assessed by applying Cox proportional models and by computing Cox-Mantel hazard ratios together with 95% CI. The assumption of proportional hazard ratios was tested by corresponding tests. The hazard ratios were tested using the Cox-Mantel Log rank test. All reported tests were two-sided, and p-values  $< 0.05$  were considered as statistically significant.

All statistical analyses in this report were performed by use of NCSS (NCSS 10, NCSS, LLC, Kaysville, UT) and STATISTICA 12 (Hill, T & Lewicki).

## Results

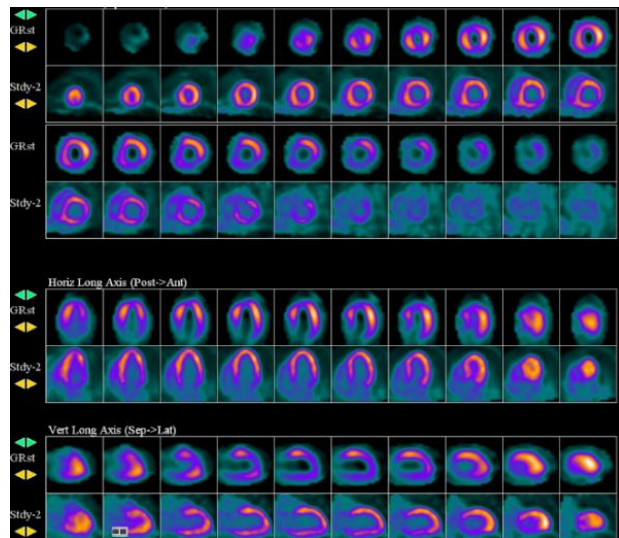
Clinical data of patients are shown in Table 1. No significant differences between diabetic and nondiabetic patients were found in clinical data (i.e. age, cigarette smoking, arterial hypertension, hyperlipidemia, renal insufficiency and LVEF) and treatment (patients that underwent revascularization and patients who received medical therapy alone).

**Table 1:** Clinical data of patients

	Patients with diabetes (n=24)	Patients without diabetes (n=56)	Patients with revascularization (n=47)	Patients with medical therapy alone (n=33)
Age (years) (range, mean)	56 – 80 (68.6)	50 – 82 (70.3)	50 – 82 (68.3)	56 – 81 (70.7)
Gender	20 male, 4 female	51 male, 5 female	43 male, 4 female	28 male, 5 female
Cigarette smoking (n=27)	9	18	19	8
Arterial hypertension (n=51)	15	36	32	19
Hyperlipidemia (n=61)	18	43	39	22
Renal insufficiency (n=16)	5	11	9	7
LVEF (%) (range, mean)	19 – 48 (35.8)	15 – 48 (31.6)	15 – 48 (33.2)	17 – 48 (31.2)

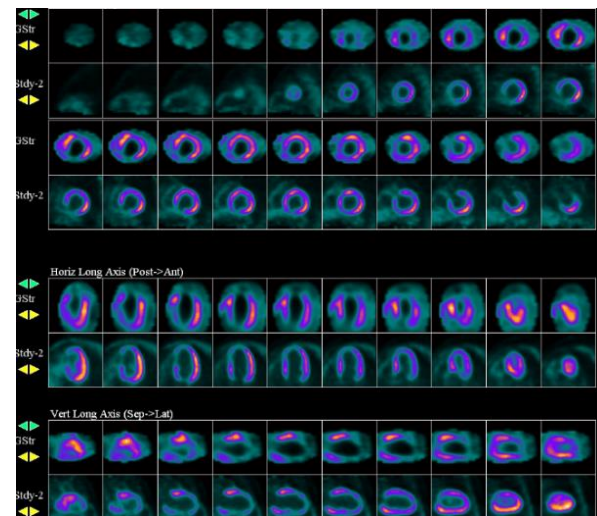
n, number of patients; LVEF, left ventricular ejection fraction

All patients had impaired LVEF (mean 32.9±9.3, range 15-48%). Diabetic patients had fewer percent of scar tissue (16.0±12.0) as compared to nondiabetic patients (25.7±18.7) (p<0.01), while the amount of hypoperfused but viable myocardium was not significantly different (14.5±12.6 vs. 9.8±12.0) (p=0.21) (Figures 1 and 2). No patient showed reverse perfusion-metabolism mismatch. In 3 out of 24 patients with diabetes, <sup>18</sup>F-DG-myo-cardial uptake was diffusely reduced which although resulted in poor-quality scans still enabled interpretation of the images and therefore further inclusion of these patients in this study.



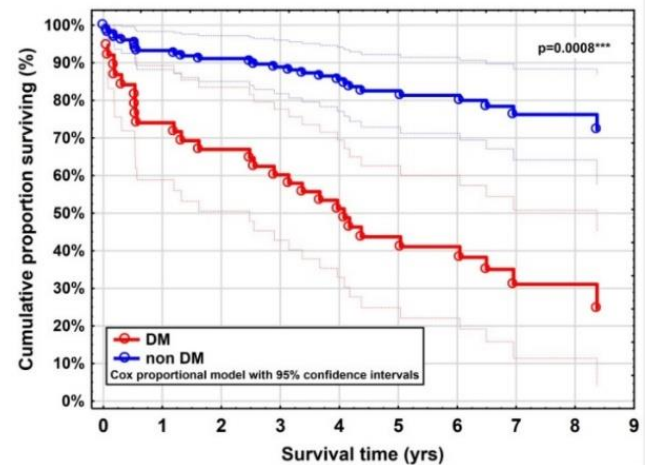
**Figure 1:** Small non-transmural scar in the anteroseptal distal wall and viable myocardium in all other segments in a 68 years old male patient with diabetes and LVEF of 27 % who died 52.8 months after myocardial viability assessment. GRst, gated rest; Stdy-2, myocardial FDG PET.

Twelve patients had angiographically documented 1 vessel disease (VD), 15 patients 2 VD, 49 patients 3 VD, and 4 patients diffuse calcification in stenotic coronary arteries. Patients with diabetes had significantly more commonly 3 VD than patients without diabetes (83% vs. 52%, p<0.01). Forty-seven patients underwent coronary revascularization [coronary-artery bypass grafting (CABG), 24 patients; stenting, 23 patients] and 33 patients' medical therapy alone. Twenty-four out of 80 patients had diabetes mellitus type II. The number of coronary revascularization procedures in patients with and without diabetes was statistically not significantly different (71% vs. 54%, p=0.55).



**Figure 2:** Large transmural scar in the apex and anterior and posterior distal wall and viable myocardium in all other segments in a 58 years old male patient without diabetes and LVEF of 29%, still alive 103.2 months after myocardial viability assessment. GRst, gated rest; Stdy-2, myocardial FDG PET.

Overall survival was 64% (51/80 patients). It was significantly favorable in patients without diabetes with a hazard ratio of 4.2 for these patients (95% CI: 1.77–9.9, p<0.001) (Figure 3).



**Figure 3:** Overall survival in patients with diabetes and patients without diabetes.

Median survival in nondiabetic patients (69.3 months, range 60.1-77.9 months) was significantly longer ( $p<0.001$ ) than that of patients with diabetes (46.5 months, range 32.7-60.3 months).

No significant survival benefit for revascularization compared to medical therapy alone using viability cut-off-points of 10%, 20%

and 30% was found both in diabetics ( $p=0.88$ ) and nondiabetic patients ( $p=0.56$ ). Longer survival was however noticed in patients with larger amounts of viable myocardium that underwent revascularization by CABG or stenting compared to patients who received medical therapy alone (Table 2).

**Table 2:** Results of survival according to myocardial viability cut-off-points

Survival	Myocardial viability					
	<10%	>10%	<20%	>20%	<30%	>30%
	n=41	n=39	n=56	n=24	n=68	n=12
Overall survival	30 (73%)	29 (74%)	42 (75%)	17 (71%)	48 (71%)	11 (92%)
Revascularized patients	13 (76%)	23 (77%)	22 (79%)	14 (74%)	27 (71%)	9 (100%)
CABG	5 (71%)	14 (82%)	10 (83%)	9 (75%)	14 (74%)	5 (100%)
Stenting	8 (80%)	9 (69%)	12 (75%)	5 (71%)	13 (68%)	4 (100%)
Medically treated only patients	17 (71%)	6 (67%)	20 (71%)	3 (60%)	21 (70%)	2 (67%)

## Discussion

Despite improvement in the management of patients with CAD, the presence of diabetes mellitus has been found to remain associated with worse outcomes [8-10]. We observed that patients with diabetes had fewer percent of scar tissue than nondiabetic patients, while the amount of hypoperfused but viable myocardium was not significantly different. Noteworthy, we found a significant death rate in the first year and a significantly shorter overall survival in the diabetic group although the LVEF values in this group were not significantly different from those found in the nondiabetic group. These findings seem to indicate diabetes as a predictor for early mortality in patients with ischemic cardiomyopathy. Furthermore, in our patient population diabetic patients had significantly more commonly 3 VD than nondiabetic patients. The presence of 3 VD may have been associated with systemic vascular disease which might have contributed to the shorter survival found in our group of patients with diabetes.

Coronary revascularization has greatly improved the outcomes of CAD patients with diabetes [9, 11]. However, much work remains to better understand the underlying mechanisms of CAD in the setting of diabetes and to improve clinical outcomes in this patient population. The development of new treatment strategies and recognition of the association between diabetes and outcomes after revascularization may help identify novel treatments for this high-risk group of patients. Two meta-analyses showed that patients with viable myocardium who underwent coronary revascularization have longer survival than those receiving medical therapy alone [12, 13]. The PARR-2 trial reported that  $^{18}\text{F}$ FDG-PET had a non-significant trend for improved outcome of coronary revascularization compared with standard care [14]. The STICH Extension Study (STICHES), which was conducted to evaluate the long-term effects of CABG in patients with ischemic cardiomyopathy found that the rates of death from cardiovascular causes, and death from any cause or hospitalization for cardiovascular causes were significantly lower over 10 years among patients who underwent CABG in addition to receiving medical therapy than among those who received medical therapy alone [15]. We found that none of the myocardial viability thresholds investigated showed significant prognostic value regarding survival for the benefit from revascularization compared to medical therapy alone. However, it is noteworthy in our study that, as the amount of myocardial viability

increases, there is a progressive increase in survival when revascularization is undertaken compared with medical therapy alone. Interestingly, this trend was more evident in patients who underwent CABG than in patients receiving stenting. Limitations of this retrospective study are the small number of patients in our subgroups. Further randomized studies with a larger number of patients are ongoing to evaluate the correlation between the amount of ischemia revascularized and the outcome after revascularization in our patient population.

Data evaluating the relationship of viability extent and outcome response to coronary revascularization are limited. Survival was found shorter when mismatch was  $>20\%$  and LVEF  $<43\%$  [16, 17]. D'Egidio et al. showed that patients with viability  $>7\%$  gained an outcome benefit when revascularization was undertaken compared with medical therapy, while in patients with viability  $<7\%$  the outcome was not significantly different [7]. In our study, no significant differences were found in overall survival or survival in coronary revascularized patients as viability increased applying myocardial viability thresholds of 10%, 20% and 30%. However, in patients receiving medically treatment only, a non-significant trend for shorter survival when the extent of viability increased was observed. These findings may be attributed to the fact that our patient population had severely reduced LVEF (mean  $32.9\pm 9.3\%$ ).

An adequate regulation of metabolic conditions is needed to ensure optimal image quality with  $^{18}\text{F}$ FDG-PET. However, insulin resistance is frequently present in patients with heart failure, and the amount of endogenous insulin released after oral glucose loading will not induce maximal stimulation of myocardial  $^{18}\text{F}$ FDG uptake [18]. Our data confirm that myocardial imaging with  $^{18}\text{F}$ FDG-PET following a euglycemic-hyperinsulinemic protocol with acipimox results in adequate imaging quality in the vast majority of diabetic patients.

## Conclusions

Ischemic cardiomyopathy patients with impaired LVEF and diabetes exhibited significantly reduced overall survival compared to patients without diabetes though they had less scarred myocardium and equal amounts of viable myocardium as indicated by  $^{18}\text{F}$ FDG-PET.

No correlation was found between overall survival (both in diabetic and nondiabetic patients) and myocardial viability thresholds of 10%, 20% or 30%.

### Conflicts of interest

There are no conflicts of interest.

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