Echocardiography

Subjects: Biotechnology & Applied Microbiology

Contributor: Konstantinos Katogiannis

Diabetes mellitus is a major factor contributing to the development of cardiovascular disease. As morbidity and mortality rates rise dramatically, when target organ damage develops, presymptomatic assessment is critical for the management of diabetic patients. Echocardiography is a noninvasive and reproductible method that may aid in risk stratification and in evaluation of treatment effects. Aim of this review is to analyze the echocardiographic techniques that can detect early alteration in cardiac function in patients with diabetes.

Echocardiography diabetes mellitus Speckle Tracking Echocardiography Doppler Echocardiography Stress Echocardiography Coronary Flow Reserve Diabetic Cardiomyopathy

1. Introduction

Diabetes mellitus (DM) enhances coronary atherosclerosis and impairs microcirculation leading to left ventricular (LV) function impairment, which is expressed as diastolic dysfunction at early stages. The ramifications of DM in the coronary circulation are quite different. In epicardial vessels, formation of atheroma is predominant, leading to luminal obliteration, thrombus formation and distal embolization. Microcirculatory disease is caused by the toxic effect of free radicals that are formulated due to persistent hyperglycemia and might provoke arteriolar thickening, perivascular myocardial fibrosis, capillary obstruction and finally endothelial dysfunction[1].

Insulin resistance and glycemic dysregulation results in left ventricular remodeling and gradually leads to impaired LV systolic and diastolic function. More specifically, DM type 2, an independent risk factor for heart failure development, can induce diabetic cardiomyopathy. In early stages of the disease, cardiac modifications include LV hypertrophy, diastolic dysfunction and decreased myocardial strain, which are precursors for the development of LV remodeling and the occurrence adverse events, including Heart failure, all-cause mortality and hospitalization[2].

This pathology may represent the reversible early stage of diabetic cardiomyopathy. Diabetic cardiomyopathy was first reported by Rubler et al.[3] in 1972 when they described four diabetic patients with heart failure, normal coronary arteries, and without obvious etiology for heart failure and stated that it was due to diabetic cardiomyopathy. Most potent mechanisms for the development of diabetic cardiomyopathy are: metabolic disturbances (increased free fatty acids, carnitine deficiency, changes in calcium homeostasis), myocardial fibrosis (increases in angiotensin II, IGF-I, and inflammatory cytokines), small vessel disease (microangiopathy, impaired coronary flow reserve [CFR] and endothelial dysfunction), autonomic neuropathy and insulin resistance[4][5].

Echocardiography is a time-sparing and cost-effective method that provides accurate and reproducible diagnostic and prognostic information in diabetic patients. By using two-dimensional, doppler and speckle tracking echocardiography, we can thoroughly interrogate cardiac function in diabetic, while stress echocardiography and evaluation of coronary flow reserve provide incremental prognostic value.

2.Diastolic Dysfunction

The prevalence of LV diastolic dysfunction in diabetic patients seems to be higher than previously reported[6], therefore the early screening for this abnormality of cardiac function is mandatory to improve prognosis of those patients. Important studies referring to diastolic dysfunction in diabetics are mentioned in table 1.

Echocardiographic abnormalities are present in patients with diabetes, despite the fact that symptoms or clinical characteristics do not mandate echocardiographic assessment. Joergensen et al studied 1030 patients with type 2 diabetes and revealed impaired cardiac function (left ventricular hypertrophy, systolic and diastolic dysfunction and dilated left atrium reflecting high filling pressures) in about 50% of them. Neither the presence of cardiac symptoms nor the patients' clinical characteristics had sufficient sensitivity and specificity to accurately identify patients with documented impaired cardiac function by echocardiography. Thus, it is recommended by official guidelines that echocardiography should be included in diagnostic evaluation of patients with type 2 diabetes even in the absence of known cardiovascular disease[7].

Moreover, diastolic dysfunction can even occur in young diabetic patients with short duration of disease. According to a recent cross-sectional study that was carried out on 86 diabetics who were compared with 65 age and sex matched controls, left ventricular diastolic dysfunction is more prevalent in diabetic patients and this was correlated independently with duration of the disease and glycated hemoglobin level. Moreover, it was claimed that diastolic dysfunction in asymptomatic patients with diabetes may represent the early stage of diabetic cardiomyopathy even in the absence of structural cardiac disease or systemic hypertension[8]. Other older studies have also reported that diastolic impairment in diabetic patients is of high prevalence[9].

Furthermore, it is claimed that LV diastolic function impairment may be noticed by echocardiography even in the first 5 years after the diagnosis of diabetes. Older studies reported that diastolic dysfunction in diabetic patients is also associated with poor glycemic control and elevated HbA1c. Hyperglycemia per se can lead to alteration in substrate supply and utilization by cardiac myocytes might represent the primary injury in the pathogenesis of diastolic function impairment and in more advanced stages diabetic cardiomyopathy[10]. Similarly, Celentano et al. reported that alteration in LV diastolic function seems to be related to level of fasting blood sugar and HbA1c even within normal limits[11], while other research group underlined that each 1% increase in HbA1c level has been associated with an 8% increase in the risk of heart failure development[12].

Another research group examined the clinical and echocardiographic characteristics of 1134 patients with diabetes (out of totally 4128 - 27%) and heart failure with preserved ejection fraction participating in the I-Preserve trial. Patients with diabetes mellitus displayed greater structural and functional echocardiographic abnormalities, had slightly larger LV dimensions and greater LV mass compared with patients without diabetes mellitus. These findings, along with the differences in mitral inflow and tissue Doppler measurements, implied increased LV stiffness, impaired LV filling and higher left atrial pressure (in concordance with higher levels of NT-proBNP) in patients with diabetes mellitus[13].

Moreover, by studying patients with DM and coronary atherosclerosis, it was concluded that there is a relationship between diastolic function deterioration, as assessed by the E/e’ ratio and structural changes in the microcirculation[1].

In individuals with type 1 diabetes without known heart disease, echocardiography significantly improves risk assessment over and above guideline-recommended clinical risk factors alone and could have a role in clinical practice. Despite current guidelines do not include routine assessment of myocardial function, it was investigated whether echocardiography provides incremental prognostic information in individuals with type 1 diabetes without known heart disease. 1093 individuals were included during 7.5 years of follow-up. Echocardiography significantly and independently predicted MACE: left ventricular ejection fraction (LVEF), impaired global longitudinal strain (GLS), diastolic mitral early velocity (E)/early diastolic tissue Doppler velocity (e′) were the main determinants of prognosis. Consequently, assessment of these markers improves the early detection of individuals in jeopardy beyond conventional clinical risk factors[14].

Moreover, left atrial evaluation is easy by echocardiography. In accordance with a recent study, left atrial enlargement in patients with DM is independent of associated hypertension and diastolic function. It seems that left atrial enlargement is associated with LA dysfunction as evaluated by 2D strain. It is likely that diabetic atrial myopathy contributes to LA enlargement in patients with DM[15].

In summary, echocardiography is likely to detect diastolic dysfunction in asymptomatic patients with diabetes, before symptoms occur. In such cases, medical treatment should be optimized, in order to prevent further devastation of heart function.

3. Global Longitudinal Strain (GLS)

Chronic abnormalities in myocardial carbohydrate and lipid metabolism due to insulin deficiency may result in reduced adenosine triphosphatase activity, decreased ability of the sarcoplasmic reticulum to take up calcium and an intracellular accumulation of toxic fatty acid intermediates. These in turn may lead to adenosine triphosphate depletion, changes in calcium homeostasis and increased myocardial oxygen consumption that may lead to myocyte hypertrophy, fibrosis development, which may affect myocardial contractility[16].

Speckle tracking echocardiography is a contemporary method that analyzes myocardial deformation. It is feasible to detect subtle myocardial impairment in diabetics, before symptoms arise and before conventional echocardiography detects malfunction. Longitudinal deformation of left ventricle is the most scrutinized mode but also radial and circumferential deformation have been thoroughly studied. Important studies referring to myocardial deformation in diabetics are mentioned in table 2.

Two-dimensional (2D) and three-dimensional (3D) speckle tracking echocardiography (STE) were used to detect preclinical diabetic cardiomyopathy in 66 asymptomatic type 1 diabetic patients with no cardiovascular risk factors, who were compared with 26 matched controls over a 6-year follow-up. Subclinical myocardial dysfunction, suggested by a mild decrease in longitudinal function, was detected by 2D and 3D-STE in type 1 diabetic patients, independently of any other cardiovascular risk factors[17].

It is common sense that DM represents a major risk factor for cardiovascular events and the coexistence of obesity with consequent left ventricular volumetric overload could be responsible for further damages on left ventricular function. Researchers sought for evidence about the effect of body mass index (BMI) on left ventricular function in diabetics with no cardiovascular complications and with normal ejection fraction (EF). In uncomplicated asymptomatic DM patients, obesity plays an incremental role in devastating left ventricular function and enhances remodeling. The conventional echocardiographic methods such as the EF and the TDI are not sensitive enough to identify subtle LV dysfunction, in contrast with Speckle Tracking echocardiography[18].

Moreover, researchers hypothesized that Galectin-3, an established biomarker in patients with heart failure with reduced ejection fraction, might be related to GLS and detect subtle left ventricular dysfunction in diabetic patients with heart failure with preserved ejection fraction. According to their results, galectin-3 was indeed elevated in diabetic patients with mildly reduced EF and was associated with a deteriorated GLS. GLS could be an early marker of left ventricular dysfunction as well as evidence of diabetic cardiomyopathy[19].

Another study aimed to investigate whether myocardial dysfunction, as assessed by GLS, is a feature of T1DM per se or it is mainly associated with complicated diabetes with albuminuria. They compared 1,065 T1DM patients without known heart disease with 198 healthy control subjects. Systolic function assessed by GLS was reduced in T1DM compared with control subjects. However, the findings do not support the presence of specific diabetic cardiomyopathy without albuminuria[20].

Moreover, the purpose of another study was to investigate whether children and adolescents with T1DM develop early asymptomatic abnormalities of left ventricular (LV) and right ventricular (RV) function. Findings claim that LV GLS and RV free wall longitudinal strain (FWLS) are impaired in children with T1DM and that the decrease in LV GLS is correlated with diabetes duration and HbA1c levels[21].

In accordance with another study, diabetic patients (type 2) showed impairment in strain and Strain Rate of LV walls at rest, especially when the duration of diabetes was increased. More precisely, strain and SR by TDI seems to be superior to conventional Doppler in early detection and evaluation of systolic and diastolic dysfunction in type 2 diabetic patients[22].

So far, evidence support that speckle tracking provides a diagnostic tool, in order preclinical myocardial dysfunction to be detected. The prognostic impact of this information was further validated by studying 247 patients with type 2 diabetes mellitus (T2DM) without history of cardiovascular complications. In this group of patients, impaired GLS was associated with cardiovascular events and provided incremental prognostic value[23].

A total of 105 subjects with type 2 diabetes mellitus and poor glycemic control received optimization of treatment for blood glucose, blood pressure, and cholesterol to recommended targets for 12 months. LV systolic and diastolic function, measured by LV global longitudinal strain (GLS) and septal e′ velocities, were compared before and after optimization. Improvements in glycemic control over a 12-month period led to improvements in LV systolic and diastolic function. This may have long-term prognostic implications[24].

Also, speckle tracking echocardiography combined with physical stress testing has been used, in order to evaluate whether left ventricular (LV) myocardial performance is altered early in the course of uncomplicated type 1 diabetes mellitus (T1DM). 40 consecutive asymptomatic normotensive children and adolescents with T1DM and 44 age- and gender-matched healthy controls were assessed by conventional and speckle tracking echocardiography (strain and strain rate) during stress testing. Despite asymptomatic T1DM patients performed hyperdynamic LV contractility early in the course of the disease, poor glycemic control was associated with early subclinical LV systolic and diastolic impairment[25].

However, a study group sought for evidence whether diabetes itself causes specific echocardiographic features of myocardial morphology and function in the absence of hypertension or ischemic heart disease. The purpose of the study was to determine the characteristics of pure diabetic cardiomyopathy-related echocardiographic morphology and function using layer-by-layer evaluation with myocardial strain echocardiography. Deterioration of left ventricular longitudinal shortening accompanied by decreased subendocardial wall thickening are the characteristic functional abnormalities of diabetic cardiomyopathy in patients without hypertrophy, diastolic dysfunction, or elevated BNP[26].

On a similar manner, 52 patients with T1DM were divided into 3 age groups, in order to detect deformation in all layers of left ventricle. Longitudinal deformation in all layers and epicardial and midmyocardial circumferential deformation at the basal level were deteriorated from the late teens and this was correlated with the duration of the disease and the presence of LV hypertrophy[27].

Moreover, in order to evaluate additive value of left atrial two-dimensional strain in patients with diabetes mellitus type 2, 218 patients with heart failure with preserved left ventricular ejection fraction were divided according to the presence of diabetes mellitus. Two-dimensional speckle tracking echocardiography appeared as a useful means of detection of left atrial dysfunction in patients with heart failure with preserved ejection fraction and diabetes mellitus, who are especially prone to develop cardiovascular complications[28].

With regard to another research group, LA deformation mechanics are impaired in patients with hypertension or diabetes with normal LA size. The coexistence of both conditions further impairs LA performance in an additive fashion. Speckle tracking echocardiography may be considered a promising tool for the early detection of LA strain abnormalities in these patients[29].

Actually, it seems that acute hyperglycemia in asymptomatic diabetic patients has significant negative effects on systolic LV myocardial mechanics primarily by reducing GLS and multilayer peak systolic longitudinal and circumferential strain which was not reversible after three months of good glycemic control[30].

Also, acute hyperglycemia postprandially seems to impair cardiac function. After studying first degree relatives of diabetics type 2 with normal oral glucose test (OGTT) and subjects with abnormal OGTT, it was concluded that post-OGTT, GLS and subendocardial Longitudinal Strain decreased while LV twisting and untwisting increased. This indicates prevalence of the motion of the subepicardial over a dysfunctioning subendocardial myocardial helix. [31]

Last but not least, according to another study, speckle tracking echocardiography could be used as to tool to monitor the effects of treatment in cardiac function. They investigated the effects of insulin, glucagon-like peptide-1 receptor agonists (GLP-1RA), sodium-glucose cotransporter-2 inhibitors (SGLT-2i) and their combination on vascular and cardiac function in 160 patients with type 2 diabetes mellitus with or without coronary artery disease. After 12 months, treatment with GLP-1RA, SGLT-2i, and their combination showed a greater improvement of effective cardiac work and myocardial deformation than insulin treatment. The combined therapy was superior to either insulin or GLP-1RA and SGLT-2i separately[32][33].

In summary, speckle tracking echocardiography might detect subtle impairment in myocardial function, which has an incremental value in risk stratification and in response to therapy in diabetic patients with or without coronary artery disease.

4. Stress Echo

Stress echocardiography is an established technique for the assessment of coronary artery disease. The combination of echocardiography with a stress test is claimed to detect myocardial ischemia with an excellent accuracy. A transient worsening of regional function during stress is the hallmark of inducible ischemia. Stress echocardiography provides similar diagnostic and prognostic accuracy as radionuclide stress perfusion imaging or magnetic resonance, but at a substantially lower cost, without environmental impact and with no biohazards for the patient and the physician. Important studies referring to stress echocardiography in diabetics are mentioned in table 3.

Stress echo is a non-invasive method that is safe for diabetic patients. The presence of segmental wall motion abnormalities during the test is an independent predictor of death, incremental to other factors, especially resting LV function. A negative stress echo in a diabetic patient is related with a higher mortality (4% per year) than in nondiabetics (1% per year). The diabetics expressing adverse cardiovascular events, despite normal stress echo result tend to be older, with deteriorated exercise capacity, and have impaired LV ejection fraction at rest. On the other hand, a positive stress echo in a diabetic is followed with a much higher annual mortality (10% per year) than in a nondiabetic (5% per year). Those with impaired LV systolic function at rest and a high ischemic burden are at greatest risk[34].

Various investigators have consistently shown that inappropriate stress echo studies do no illustrate any prognostic significance[35].

A recent study evaluated the prognostic impact of appropriateness criteria in diabetic patients, with known or suspected CAD and concluded that dobutamine stress echo is a strong prognostic predictor in diabetics with appropriate indication. However, the presence of diabetes had no impact on the prognosis of patients deemed as inappropriate for DSE. The authors suggest that appropriateness criteria show discriminating ability in diabetics and emphasize the importance of adhering to appropriateness criteria. Therefore, the clinician should not refer inappropriate patients for stress echo evaluation of even if they are diabetics[36]. The European Society of Cardiology (ESC) Task Force recommends the use of noninvasive testing for risk stratification of diabetic patients with known or suspected coronary artery disease (CAD), which should be performed according to individual needs and clinical judgment and not meant as a general recommendation to be undertaken by all patients. However, stress testing or CTCA may be indicated in very high-risk asymptomatic individuals [with peripheral arterial disease (PAD), a high CAC score, proteinuria, or renal failure][37].

In fact, in asymptomatic subjects, routine screening for CAD is controversial.

Moreover, a research group tried to determine the prognostic value of dobutamine stress echocardiography (DSE) for predicting long-term outcomes in a large cohort of 2,349 patients with diabetes mellitus. Addition of stress echocardiographic variables to the clinical and rest echocardiographic model provided incremental prognostic information for predicting mortality and morbidity. In patients with diabetes mellitus, a simple and practical risk score using clinical variables and results of DSE stratified patients into three risk groups for mortality and cardiovascular morbidity[38].

Similarly, another study claimed that stress echocardiography is an elaborative method to evaluate cardiovascular risk in diabetic patients with coronary artery disease. They assessed the prognostic significance of pharmacological stress echocardiography in 325 diabetic patients with suspected coronary artery disease during a follow-up period of 34 months. Despite the fact that univariate analysis indicated an increased risk of cardiovascular death from a positive response in stress test, multivariate analysis showed that only advanced age and peak ejection fraction <40% were independent predictors of cardiac death. After dividing the population into two subgroups on the basis of EF at rest, only a peak EF <40% and a pharmacological stress echocardiography positive test were powerful independent predictors of cardiovascular mortality[39].

Moreover, due to the fact that coronary artery disease is the leading cause of death in diabetic patients, scientists search for methods that evaluate the risk of adverse cardiac events. 193 diabetic patients were recruited and followed-up during a median period of 29 months. Patients with findings of ischemia on Exercise Echocardiography

(EE) presented higher rates of cardiac events at 12 months. In the present study, the number of positive EE was higher than reported in the general population, confirming the higher risk of CAD in diabetic patients and revealing that EE is a useful method to predict cardiac events in diabetic patients with suspected or known CAD.

Ischemia at stress echocardiography, performed for evaluation of known or suspected coronary artery disease, is a strong and independent predictor of total mortality in diabetic as well as in nondiabetic patients. Anti-ischemic therapy markedly affects the negative predictive value of stress echocardiography in nondiabetic patients, whereas it is prognostically neutral in the diabetic population.

The results of a recent study indicate that stress echocardiography is a useful prognostic tool in diabetic patients. A normal study with any type of stressor is a marker of low risk; however, in the diabetic group, the risk is higher. Inducible ischemia at stress echocardiography is an independent predictor of mortality in all patients, despite being diabetics or not, and the level of risk is related to the extent of the inducible abnormality as expressed by peak WMSI[40]. Also, medical treatment during the test provides a higher risk in nondiabetics, in spite of not having prognostic role in diabetics[41].

The coexistence of epicardial coronary artery stenosis with microangiopathy can explain the low specificity of perfusion imaging compared to stress echocardiography in the detection of CAD in asymptomatic and symptomatic diabetic patients. In diabetic patients, stress echocardiography has shown a higher specificity than perfusion imaging but suffers from higher rate of false positive results, possibly due to the coexistence of cardiomyopathy in many patients. in diabetic patients – differently from nondiabetic subjects – a negative test result based solely on wall motion criteria is associated with less benign outcome[42].

Seeking for evidence which diabetic patients should be screened for cardiovascular disease remains difficult. It seems that only 5%–10% of asymptomatic diabetics have obstructive CAD and as a result screening of all diabetics is inappropriate. However, certain group of diabetic patients, such as those who need pancreas/renal transplantation[43] or major noncardiac surgery[44] may benefit from a stress echo. However, diabetics with cardiac symptoms, even if atypical, and those with known or suspected CAD warrant screening and prognostic evaluation[35].

Furthermore, in patients with diabetes, the role of stress echo in diagnostic screening of CAD remains controversial. Conventional wall motion analysis and Doppler-derived coronary flow reserve (CFR) of the left anterior descending coronary artery were evaluated in high- risk asymptomatic individuals with diabetes (target organ damage or two or more cardiovascular risk factors). Abnormal test results were obtained in 25% of cases and were a strong and independent predictor of future hard events and MACEs[45].

A recent study which evaluated the long-term predictive value of dobutamine stress echocardiography provided restricted predictive value of adverse outcome in patients with diabetes who were unable to perform an adequate exercise stress test. Also, it was suggested that there is a period of up to 7 years after the test, that optimal risk stratification is provided[46].

Finally, according to another study, low dose DB unmasked linear deformations and twist mechanics abnormalities that were otherwise undetectable at rest. They prospectively investigated forty-four patients with T2DM and 35 healthy control subjects of similar age and sex. Deformation imaging indexes were similar between groups at rest, but significant differences were noticed under dobutamine infusion for longitudinal strain, circumferential strain, rotation and twist[47].

In summary, stress echocardiography is a valuable tool for the management of diabetic patients. Diagnosis of coronary artery disease and risk stratification are feasible by stress echocardiography, when clinicians comply with appropriateness criteria.

5. CFR

Echocardiography, apart from unveiling preclinical myocardial dysfunction in asymptomatic patients with diabetes, may further contribute to the risk stratification of diabetic patients. Innovative and state-of-the art methods, such as Coronary Flow Reserve Assessment by Doppler Echocardiography may detect endothelial dysfunction and deterioration of microvascular circulation that is probably associated with the severity of diabetes ramifications. Important studies referring to coronary flow reserve in diabetics are mentioned in table 4.

The role of CFR in risk stratification of asymptomatic diabetic patients is crucial. Researchers that investigated asymptomatic patients with type 2 diabetes without a history of coronary artery disease concluded that CFR, obtained by transthoracic Doppler echocardiography, provides an independent prognostic marker in these patients. After excluding patients with a CFR < 2.0 because of a suspicion of significant coronary artery stenosis in the left anterior descending artery, the optimal cut-off value of CFR to predict events was 2.5. Compared with CFR ≥ 2.5, patients with CFR < 2.5 had significantly worse outcome[48].

Also, other investigators studied patients admitted in hospital due to chest pain and suspected coronary artery disease. Among them, diabetic patients had more significant aortic atherosclerosis and lower CFR, while significant CAD was more common in diabetics. CFR and diabetes were independent predictors of cardiovascular survival. Patients with reduced CFR (impaired microcirculatory function) and DM had the worst prognosis[49].

Another group of researchers sought to determine the coronary microvascular function of prediabetic patients in comparison with diabetic patients and normal population. CFR values of DM group were lower than those of prediabetic and control groups. However, CFR levels of prediabetic group were not different from those of the control group. Coronary microvascular function seems to be normal in the prediabetic state, but dysfunction appears after DM becomes overt[50].

In a similar way, it was investigated whether first degree relatives of diabetics have also deteriorated coronary microcirculation, LV myocardial strain and twisting with patients with diabetes as assessed after an oral glucose tolerance test (OGTT). Indeed, first degree relatives and diabetics have increased arterial stiffness, impaired wave reflection and diminished CFR compared to normals with regard to insulin resistance, while insulin resistance was also associated with abnormal LV myocardial strain, twisting and untwisting likely because of increased arterial stiffness and impaired coronary microcirculatory function[51].

Moreover, the differences in coronary flow reserve of diabetic patients with and without diabetic retinopathy is of great importance. It is claimed that coronary flow reserve is significantly restricted in patients with diabetes mellitus and its reduction is more remarkable in those with diabetic retinopathy. Coronary microvascular impairment should be considered as an explanation for this restricted coronary flow reserve in patients with diabetes mellitus and this should be more remarkable in patients with target organ damage. The more advanced the development of retinopathy, the more exaggerated the impairment in microvascular function, as assessed by coronary flow reserve[52].

In normotensive patients with insulin treated diabetes (DP) with clinically suspected coronary heart disease but normal epicardial coronary arteries, coronary microcirculation was studied. In diabetic patients, maximal coronary flow was significantly reduced. Global systolic function was normal in all patients. Diastolic function was impaired in diabetics. The reduced coronary flow reserve in patients with insulin-treated diabetes mellitus may play a crucial role in the pathophysiology of diabetic cardiopathy, causing myocardial ischemia due to a disturbance of coronary microcirculation leading to diastolic dysfunction and progressively to systolic failure[53].

To clarify if coronary flow reserve (CFR) is related to insulin resistance or hyperglycemia in normotensive non-insulin dependent diabetic (NIDDM), myocardial blood flow at baseline and during dipyridamole loading were measured. CFR was significantly reduced in NIDDM patients compared with age matched control subjects. CFR in patients with well-controlled NIDDM was significantly higher than in those with poorly controlled NIDDM, whereas insulin resistance was comparable between the two groups. In conclusion, control of blood glucose concentration rather than insulin resistance is most likely related to the reduced CFR in NIDDM[54].

In summary, CFR has important role in the diagnosis of endothelial and microvascular dysfunction in diabetics, while combined with stress echocardiography has incremental role in the diagnosis and risk stratification of coronary artery disease.

6. Conclusion

Proper assessment of diabetic patients is critical, in order to hamper the development of vascular and microvascular complications. Echocardiography is a feasible and safe method that provides diagnostic and prognostic information in patients with diabetes mellitus. A diversity of applications, such as Doppler echocardiography, Speckle Tracking Echocardiography and Stress Echocardiography could be useful for the management of diabetics and the optimization of medical treatment. Contemporary standard of care in diabetics should include echocardiography for their clinical assessment.

References

1. Escaned J, Colmenárez H, Ferrer MC, Gutiérrez M, Jiménez-Quevedo P, Hernández R, Alfonso F, Bañuelos C, Deisla LP, Zamorano JL, Macaya C. Diastolic dysfunction in diabetic patients assessed with Doppler echocardiography: relationship with coronary atherosclerotic burden and microcirculatory impairment. Rev Esp Cardiol. 2009 Dec;62(12):1395-403. doi: 10.1016/s1885-5857(09)73534-0.
2. Ernande L, Audureau E, Jellis CL, Bergerot C, Henegar C, Sawaki D, Czibik G, Volpi C, Canoui-Poitrine F, Thibault H, Ternacle J, Moulin P, Marwick TH, Derumeaux G. Clinical Implications of Echocardiographic Phenotypes of Patients With Diabetes Mellitus. J Am Coll Cardiol. 2017 Oct 3;70(14):1704-1716. doi: 10.1016/j.jacc.2017.07.792.
3. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown The incidence of congestive heart failure in type 2 diabetes: an update. Diabetes Care. 2004;27:1879–84. doi: 10.2337/diacare.27.8.1879.
4. Dries DL, Sweitzer NK, Drazner MH, Stevenson LW, Gersh BJ. Prognostic impact of diabetes mellitus in patients with heart failure according to the etiology of left ventricular systolic dysfunction. J Am Coll Cardiol. 2001;38:421–8. doi: 10.1016/S0735-1097(01)01408-5.
5. Jaarsma T, Van der Wal MH, Lesman-Leegte I. for the COACH Study Group et al.Effect of moderate or intensive disease management program on outcome in patients with heart failure. The Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure (COACH) Arch Intern Med. 2008;168:316–24. doi: 10.1001/archinternmed.2007.83.
6. Grigorescu ED, Lacatusu CM, Floria M, Mihai BM, Cretu I, Sorodoc L. Left Ventricular Diastolic Dysfunction in Type 2 Diabetes-Progress and Perspectives. Diagnostics (Basel). 2019;9(3):121. Published 2019 Sep 17. doi:10.3390/diagnostics9030121.
7. Jørgensen PG, Jensen MT, Mogelvang R, von Scholten BJ, Bech J, Fritz-Hansen T, Galatius S, Biering-Sørensen T, Andersen HU, VilsbøllT, Rossing P, Jensen JS. Abnormal echocardiography in patients with type 2 diabetes and relation to symptoms and clinical characteristics. Diab Vasc Dis Res. 2016 Sep;13(5):321-30. doi: 10.1177/1479164116645583.
8. Ashour K (2018) Early Detection of Diastolic Dysfunction in Diabetic Patients (Single Center Cross Sectional Study). J Heart Cardiovasc Res. Vol.2 No.1:3.
9. Saunders J, Mathewkutty S, Drazner MH, McGuire DK. Cardiomyopathy in type 2 diabetes: update on pathophysiological mechanisms. Herz. 2008;33:184–90. doi: 10.1007/s00059-008-3115-3.
10. Romano S, Di Mauro M, Fratini S, Guarracini L Guarracini F, Poccia G, Penco M. Early diagnosis of left ventricular diastolic dysfunction in diabetic patients: a possible role for natriuretic peptides. Cardiovasc Diabetol. 2010; 9: 89. doi: 10.1186/1475-2840-9-89.

11. Celentano A, Vaccaro O, Tammaro P, Galderisi M, Crivaro M, et al. (1995) Early abnormalities of cardiac function in non-insulindependent diabetes mellitus and impaired glucose tolerance. Am J Cardiol. 1995 Dec 1;76(16):1173-6. doi: 10.1016/s0002-9149(99)80330-0.
12. Ponikowski P, Voors AA, Anker SD (2016) ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 18: 891-975.
13. Kristensen SL, Mogensen UM, Jhund PS, Petrie MC, Preiss D, Win S, Køber L, McKelvie RS, Zile MR, Anand IS, Komajda M, Gottdiener JS, Carson PE, McMurray JJ. Clinical and Echocardiographic Characteristics and Cardiovascular Outcomes according to Diabetes Status in Patients With Heart Failure and Preserved Ejection Fraction: A Report From the I-Preserve Trial (Irbesartan in Heart Failure With Preserved Ejection Fraction). Circulation. 2017 Feb 21;135(8):724-735. doi: 10.1161/CIRCULATIONAHA.116.024593.
14. Jensen MT, Sogaard P, Gustafsson I, Bech J, Hansen TF, Almdal T, Theilade S, Biering-Sørensen T, Jørgensen PG, Galatius S, Andersen HU, Rossing P. Echocardiography improves prediction of major adverse cardiovascular events in a population with type 1 diabetes and without known heart disease: the Thousand & 1 Study. Diabetologia. 2019 Dec;62(12):2354-2364. doi: 10.1007/s00125-019-05009-2.
15. Kadappu KK, Boyd A, Eshoo S, Haluska B, Yeo AE, Marwick TH, Thomas L. Changes in left atrial volume in diabetes mellitus: more than diastolic dysfunction? Eur Heart J Cardiovasc Imaging. 2012 Dec;13(12):1016-23. doi: 10.1093/ehjci/jes084.
16. Fang ZY, Yuda S, Anderson V, Short L, Case C, Marwick TH. Echocardiographic detection of early diabetic myocardial disease. J Am Coll Cardiol. 2003 Feb 19;41(4):611-7.
17. Ringle A, Dornhorst A, Rehman MB, Ruisanchez C, Nihoyannopoulos P. Evolution of subclinical myocardial dysfunction detected by two-dimensional and three-dimensional speckle tracking in asymptomatic type 1 diabetic patients: a long term follow-up study. Echo Res Pract. 2017 Dec; 4(4): 73–81. doi: 10.1530/ERP-17-0052.
18. Conte L, Fabiani I, Barletta V, Bianchi C, Ciccarone AM, Cucco C, De Filippi M, Miccoli R, Del Prato S, Palombo C, Di Bello Early Detection of Left Ventricular Dysfunction in Diabetes Mellitus Patients with Normal Ejection Fraction, Stratified by BMI: A Preliminary Speckle Tracking Echocardiography Study. J Cardiovasc Echogr. 2013 Jul-Sep; 23(3): 73–80. doi: 10.4103/2211-4122.123953.
19. Flores-Ramírez R, Azpiri-López JR, González-González JG, Ordaz-Farías A, González-Carrillo LE, Carrizales-Sepúlveda EF, Vera-Pineda R. Global longitudinal strain as a biomarker in diabetic cardiomyopathy. A comparative study with Gal-3 in patients with preserved ejection fraction. Arch Cardiol Mex. 2017 Oct - Dec;87(4):278-285. doi: 10.1016/j.acmx.2016.06.002.

20. Jensen MT, Sogaard P, Andersen HU, Bech J, Fritz Hansen T, Biering-Sørensen T, Jørgensen PG, Galatius S, Madsen JK, Rossing P, Jensen JS. Global longitudinal strain is not impaired in type 1 diabetes patients without albuminuria: the Thousand & 1 study. JACC Cardiovasc Imaging. 2015 Apr;8(4):400-410. doi: 10.1016/j.jcmg.2014.12.020.
21. Zairi I, Mzoughi K, Kamoun S, Moussa FB, Rezgallah R, Maatoug J, Mazigh S, Kraiem S. Impairment of left and right ventricular longitudinal strain in asymptomatic children with type 1 diabetes. Indian Heart J. 2019 May-Jun; 71(3): 249–255. doi: 10.1016/j.ihj.2019.04.008.
22. Mohamed M. Assessment of left ventricular functions by strain and strain rate echocardiography in asymptomatic type II diabetic patients. Al-Azhar Assiut Med J 2019; 17 (2):119-131. doi: 10.4103/AZMJ.AZMJ_16_18.
23. Liu JH, Chen Y, Yuen M, Zhen Z, Chan CW, Lam KS, Tse HF, Yiu KH. Incremental prognostic value of global longitudinal strain in patients with type 2 diabetes mellitus. Cardiovasc Diabetol. 2016 Feb 3;15:22. doi: 10.1186/s12933-016-0333-5.
24. Leung M, Wong VW, Hudson M, Leung DY. Impact of Improved Glycemic Control on Cardiac Function in Type 2 Diabetes Mellitus. Circ Cardiovasc Imaging. 2016 Mar;9(3):e003643. doi: 10.1161/CIRCIMAGING.115.003643.
25. Hensel KO, Grimmer F, Roskopf M, Jenke AC, Wirth S, Heusch A. Subclinical Alterations of Cardiac Mechanics Present Early in the Course of Pediatric Type 1 Diabetes Mellitus: A Prospective Blinded Speckle Tracking Stress Echocardiography Study. J Diabetes Res. 2016;2016:2583747. doi: 10.1155/2016/2583747.
26. Enomoto M, Ishizu T, Seo Y, Yamamoto M, Suzuki H, Shimano H, Kawakami Y, Aonuma K. Subendocardial Systolic Dysfunction in Asymptomatic Normotensive Diabetic Patients. Circ J. 2015;79(8):1749-55. doi: 10.1253/circj.CJ-15-0012.
27. Iso T, Takahashi K, Yazaki K, Ifuku M, Nii M, Fukae T, Yazawa R, Ishikawa A, Haruna H, Takubo N, Kurita M, Ikeda F, Watada H, Shimizu T. In-Depth Insight Into the Mechanisms of Cardiac Dysfunction in Patients With Type 1 Diabetes Mellitus Using Layer-Specific Strain Analysis. Circ J. 2019 May 24;83(6):1330-1337. doi: 10.1253/circj.CJ-18-1245.
28. Georgievska-Ismail L, Zafirovska P, Hristovski Z. Evaluation of the role of left atrial strain using two-dimensional speckle tracking echocardiography in patients with diabetes mellitus and heart failure with preserved left ventricular ejection fraction. Diab Vasc Dis Res. 2016 Nov;13(6):384-394. doi: 10.1177/1479164116655558.
29. Mondillo S, Cameli M, Caputo ML, Lisi M, Palmerini E, Padeletti M, Ballo P. Early detection of left atrial strain abnormalities by speckle-tracking in hypertensive and diabetic patients with normal left atrial size. J Am Soc Echocardiogr. 2011 Aug;24(8):898-908. doi: 10.1016/j.echo.2011.04.014.

30. Bogdanović J, Ašanin M, Krljanac G, Lalić N, Jotić A, Stanković S, Rajković N, Stošić L, Rasulić I, Milin J, Popović D, Bogdanović L, Lalić K. Impact of acute hyperglycemia on layer-specific left ventricular strain in asymptomatic diabetic patients: an analysis based on two-dimensional speckle tracking echocardiography. Cardiovasc Diabetol. 2019 Jun 3;18(1):68. doi: 10.1186/s12933-019-0876-3.
31. Ikonomidis I, Pavlidis G, Lambadiari V, Kousathana F, Varoudi M, Spanoudi F, Maratou E, Parissis J, Triantafyllidi H, Dimitriadis G, Lekakis J. Early detection of left ventricular dysfunction in first-degree relatives of diabetic patients by myocardial deformation imaging: The role of endothelial glycocalyx damage. Int J Cardiol. 2017 Apr 15;233:105-112. doi: 10.1016/j.ijcard.2017.01.056.
32. Ikonomidis, I., Pavlidis, G., Thymis, J., Birba, D., Kalogeris, A., Kousathana, F., Kountouri, A., Balampanis, K., Parissis, J., Andreadou, I., Katogiannis, K., Dimitriadis, G., Bamias, A., Iliodromitis, E., & Lambadiari, V. (2020). Effects of Glucagon-Like Peptide-1 Receptor Agonists, Sodium-Glucose Cotransporter-2 Inhibitors, and Their Combination on Endothelial Glycocalyx, Arterial Function, and Myocardial Work Index in Patients With Type 2 Diabetes Mellitus After 12-Month Treatment. Journal of the American Heart Association, 9(9), e015716. https://doi.org/10.1161/JAHA.119.015716.
33. Lambadiari, V., Pavlidis, G., Kousathana, F., Maratou, E., Georgiou, D., Andreadou, I., Kountouri, A., Varoudi, M., Balampanis, K., Parissis, J., Triantafyllidi, H., Katogiannis, K., Birba, D., Lekakis, J., Dimitriadis, G., & Ikonomidis, I. (2019). Effects of Different Antidiabetic Medications on Endothelial Glycocalyx, Myocardial Function, and Vascular Function in Type 2 Diabetic Patients: One Year Follow-Up Study. Journal of clinical medicine, 8(7), 983. https://doi.org/10.3390/jcm8070983.
34. Sharma R, Pellerin D. Stress echocardiogaphy: a useful test for assessing cardiac risk in diabetes. Vasc Health Risk Manag. 2009;5(1):1-7.
35. Bhattacharyya S, Kamperidis V, Chahal N, Shah BN, Roussin I, Li W, Khattar R, Senior R. Clinical and prognostic value of stress echocardiography appropriateness criteria for evaluation of coronary artery disease in a tertiary referral center. Heart. 2014; 100: 370-374.
36. Aggeli C, Felekos I, Angelis A, Toutouzas K, Tousoulis D. Dobutamine stress echo in diabetics: Changes in prognosis according to appropriateness criteria indication. Int J Cardiol. 2016 Jul 1;214:207-8. doi: 10.1016/j.ijcard.2016.03.179.
37. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020 Jan 14;41(3):407-477. doi: 10.1093/eurheartj/ehz425.

38. Chaowalit N, Arruda AL, McCully RB, Bailey KR, Pellikka PA. Dobutamine stress echocardiography in patients with diabetes mellitus: enhanced prognostic prediction using a simple risk score. J Am Coll Cardiol. 2006 Mar 7;47(5):1029-36. doi: 10.1016/j.jacc.2005.10.048.
39. D'Andrea A, Severino S, Caso P, De Simone L, Liccardo B, Forni A, Pascotto M, Di Salvo G, Scherillo M, Mininni N, Calabrò R. Prognostic value of pharmacological stress echocardiography in diabetic patients. Eur J Echocardiogr. 2003 Sep;4(3):202-8. doi:10.1016/S1525-2167(02)00165-8.
40. Bigi R, Desideri A, Cortigiani L, Bax JJ, Celegon L, Fiorentini C. Stress echocardiography for risk stratification of diabetic patients with known or suspected coronary artery disease. Diabetes Care. 2001 Sep;24(9):1596-601. doi: 10.2337/diacare.24.9.1596.
41. Cortigiani L, Borelli L, Raciti M, Bovenzi F, Picano E, Molinaro S, Sicari R. Prediction of mortality by stress echocardiography in 2835 diabetic and 11305 nondiabetic patients. Circ Cardiovasc Imaging. 2015 May;8(5). pii: e002757. doi: 10.1161/CIRCIMAGING.114.002757.
42. Sicari R, Cortigiani L. The clinical use of stress echocardiography in ischemic heart disease. Cardiovasc Ultrasound. 2017 Mar 21;15(1):7. doi: 10.1186/s12947-017-0099-2.
43. Bates JR, Sawada SG, Segar DS, Spaedy AJ, Petrovic O, Fineberg NS, Feigenbaum H, Ryan T. Evaluation using dobutamine stress echocardiography in patients with insulin-dependent diabetes mellitus before kidney and/or pancreas transplantation. Am J Cardiol. 1996 Jan 15;77(2):175-9. doi: 10.1016/s0002-9149(96)90591-3.
44. Poldermans D, Arnese M, Fioretti PM, et al. Improved cardiac risk stratification in major vascular surgery with dobutamine-atropine stress echocardiography. J Am Coll Cardiol. 1995;26:648–53.
45. Cortigiani L, Gherardi S, Faggioni M, Bovenzi F, Picano E, Petersen C, Molinaro S, Sicari R. Dual-Imaging Stress Echocardiography for Prognostic Assessment of High-Risk Asymptomatic Patients with Diabetes Mellitus. J Am Soc Echocardiogr. 2017 Feb;30(2):149-158. doi: 10.1016/j.echo.2016.10.003.
46. van der Sijde JN, Boiten HJ, Sozzi FB, Elhendy A, van Domburg RT, Schinkel AF. Long-term prognostic value of dobutamine stress echocardiography in diabetic patients with limited exercise capability: a 13-year follow-up study. Diabetes Care. 2012;35:634–9.
47. Philouze C, Obert P, Nottin S, Benamor A, Barthez O, Aboukhoudir F. Dobutamine Stress Echocardiography Unmasks Early Left Ventricular Dysfunction in Asymptomatic Patients with Uncomplicated Type 2 Diabetes: A Comprehensive Two-Dimensional Speckle-Tracking Imaging Study. J Am Soc Echocardiogr. 2018 May;31(5):587-597. doi: 10.1016/j.echo.2017.12.006.
48. Kawata T, Daimon M, Hasegawa R, Toyoda T, Sekine T, Himi T, Uchida D, Miyazaki S, Hirose K, Ichikawa R, Maruyama M, Suzuki H, Daida H. Prognostic value of coronary flow reserve assessed by transthoracic Doppler echocardiography on long- term outcome in asymptomatic

patients with type 2 diabetes without overt coronary artery disease. Cardiovasc Diabetol. 2013 Aug 27;12:121. doi: 10.1186/1475-2840-12- 21.

49. Nemes A, Forster T, Geleijnse ML, Kutyifa V, Neu K, Soliman OI, Ten Cate FJ, Csanády M. The additional prognostic power of diabetes mellitus on coronary flow reserve in patients with suspected coronary artery disease. Diabetes Res Clin Pract. 2007 Oct;78(1):126-31. doi: 10.1016/j.diabres.2007.03.002.
50. Atar AI, Altuner TK, Bozbas H, Korkmaz ME. Coronary flow reserve in patients with diabetes mellitus and prediabetes. Echocardiography. 2012 Jul;29(6):634-40. doi: 10.1111/j.1540-8175.2012.01668.x.
51. Ikonomidis I, Lambadiari V, Pavlidis G, Koukoulis C, Kousathana F, Varoudi M, Spanoudi F, Maratou E, Parissis J, Triantafyllidi H, Paraskevaidis I, Dimitriadis G, Lekakis J. Insulin resistance and acute glucose changes determine arterial elastic properties and coronary flow reserve in dysglycaemic and first-degree relatives of diabetic patients. Atherosclerosis. 2015 Aug;241(2):455-62. doi: 10.1016/j.atherosclerosis.2015.06.006.
52. Akasaka T, Yoshida K, Hozumi T, Takagi T, Kaji S, Kawamoto T, Morioka S, Yoshikawa J. Retinopathy identifies marked restriction of coronary flow reserve in patients with diabetes mellitus. J Am Coll Cardiol. 1997 Oct;30(4):935-41. doi: 10.1016/s0735-1097(97)00242-8.
53. Strauer BE, Motz W, Vogt M, Schwartzkopff B. Evidence for reduced coronary flow reserve in patients with insulin-dependent diabetes. A possible cause for diabetic heart disease in man. Exp Clin Endocrinol Diabetes. 1997;105(1):15-20. doi: 10.1055/s-0029-1211722.
54. Yokoyama I, Ohtake T, Momomura S, Yonekura K, Woo-Soo S, Nishikawa J, Sasaki Y, Omata M. Hyperglycemia rather than insulin resistance is related to reduced coronary flow reserve in NIDDM. Diabetes. 1998 Jan;47(1):119-24. doi: 10.2337/diab.47.1.119.