SEMMELWEIS UNIVERSITY OF MEDICINE

Relationship between Insulin Resistance and Left Ventricular Diastolic Dysfunction

Ph.D. dissertation

Gani Bajraktari, M.D.

Supervisor: Prof. Ferenc Horkay, M.D., Ph.D.

Budapest, Hungary, 2006

ABBREVIATIONS

DM- diabetes mellitus

WHO - World Health Organization

CAD - coronary artery disease

IR - Insulin resistance

FPG - fasting plasma glucose

IGT - impaired glucose tolerance

NGT - normal glucose tolerance

HOMA-IR - Homeostasis Model Assessment of Insulin Resistance

QUICKI - Quantitative Insulin Sensitivity Check Index

MMP-matrix metalloproteinase

TIMP-tissue inhibitor of matrix metalloproteinase

SR-sarcoplasmic reticulum

Tn-C – troponin C

Tn-I – troponin I

HDL - high density lipoproteins

LDL - low density lipoproteins

VLDL - very low density lipoproteins

OGTT - oral glucose tolerance test

RIA - radioimmunoassay

E - maximal early filling velocity

A - maximal late (atrial) filling velocity

E/A - ratio between E and A waves

DT-E - deceleration time of E wave

LV - left ventricle

BMI- body/mass index

SBP-systolic blood pressure;

DBP-diastolic blood pressure

TGF-ß1- transforming growth factor beta-1

1. INTRODUCTION

1.1 Diabetes mellitus

Diabetes mellitus (DM) is one of the most prevalent metabolic disorders in the world, and in fact in many regions in the world it is actually the most common metabolic disorder (1). It comprises a group of common metabolic disorders that share the phenotype of hyperglycemia, due to absolute or relative deficiency of insulin (2, 3). It is estimated that that the number of diabetic patients worldwide has already exceeded 200 million (4). Global estimates for the year 2010 predict a further growth of almost 50% (5). In more developed societies, the prevalence of DM has reached the level of about 6% (6). Poorly controlled or undiagnosed disease may be associated with so called late complications of DM, such as accelerated atherosclerosis, blindness, renal insufficiency, stroke and vascular diseases (1, 2). The overwhelming complications of diabetes mellitus are mostly macrovascular and microvascular diseases as a consequence of accelerated atherogenesis. Cardiovascular morbidity in patients with type 2 diabetes is two to four times greater than that of non-diabetic people (5). Diabetes is also associated with a decrease of life expectancy (1, 5). These facts make diabetes a major health problem. There are two main forms of diabetes: type 1 and type 2 diabetes (2, 3). Diabetes mellitus is diagnosed on the basis of World Health Organization (WHO) recommendations from 1999, incorporating both fasting and 2-h after glucose load (75g) criteria (7).

1.2 Type 2 diabetes

Type 2 diabetes is prevalent in about 90% of diabetic individuals, previously known as non-insulin dependent diabetes mellitus (4, 5). Type 2 diabetes is characterized by the presence of two abnormalities: impairment of insulin secretion and decrease in insulin sensitivity (8). Although lifestyle and overeating seem to be the triggering pathogenic

factors, genetic elements are also involved in the pathogenesis of type 2 diabetes (9). Individuals with positive family history have 2-4 fold increased risk for type 2 diabetes, whereas 15-20% of first-degree relatives of patients with type 2 diabetes develop impaired glucose tolerance or diabetes (10). If one parent had type 2 diabetes, the lifetime risk (at age 80 years) for type 2 diabetes has been calculated to be 38% (10), whereas the prevalence of type 2 diabetes in the offspring is estimated to approach 60% by the age of 60 years, if both parents are affected (11).

1.2.1 Pathophysiology of hyperglycaemia

Insulin is the key hormone for regulation of blood glucose and, generally, normoglycaemia is maintained by the balanced interplay between insulin action and insulin secretion. Insulin was discovered in 1921 by Dr. Banting (a surgeon from Toronto), assisted by medical student Best, and under the supervision of McLeod, Professor of Carbohydrate Metabolism. They administered chilled saline extracts of pancreas intravenously to dogs rendered diabetic by pancreatectomy and observed lowering of blood glucose (12). Before this, in 1889 German scientists Minkowski and von Mering noted, from their experimental work with animals, that total pancreatectomy led to the development of severe diabetes (13). In 1928, insulin was found to be a polypeptide with its amino acid sequence identified in 1952. It is in fact a di-polypeptide, containing A and B chains respectively, linked by disulphide bridges, and containing 51 amino acids, with a molecular weight of 5802. Its iso-electric point is pH 5.5 (14). The A chain comprises 21 amino acids and the B chain 30 amino acids. The A chain has an N-terminal helix linked to an anti-parallel C-terminal helix; the B chain has a central helical segment. The two chains are joined by 2 disulphide bonds, which join the N- and C-terminal helices of the A chain to the central helix of the B chain. In pro-insulin, a connecting peptide links the N-terminus of the A chain to the C-terminus of the B chain (15). Insulin is coded on the short arm of chromosome 11 and synthesized in the β cells of the pancreatic islets of Langherhans as its precursor, proinsulin (16). Proinsulin is synthesized in the ribosomes of the rough endoplasmic reticulum (RER) from mRNA as pre-proinsulin. Pre-proinsulin is formed by sequential synthesis of a signal

peptide, the B chain, the connecting C-peptide and then the A chain comprising a single chain of 100 amino acids. Removal of the signal peptide forms proinsulin, which acquires its characteristic 3 dimensional structure in the endoplasmic reticulum. Secretory vesicles transfer proinsulin from the endoplasmatic reticulum to the Golgi apparatus, whose aqueous zinc and calcium rich environment favours formation of soluble zinc-containing proinsulin hexamers.6 As immature storage vesicles form from the Golgi apparatus, enzymes acting outside the Golgi apparatus convert proinsulin to insulin and C-peptide (13). Insulin forms zinc-containing hexamers which are insoluble, precipitating as chemically stable crystals at pH 5.5. When mature granules are secreted into the circulation by exocytosis, insulin, and an equimolar ratio of C-peptide are released. Proinsulin and zinc typically comprise no more than 6% of the islet cell secretion (15). Increased levels of glucose induce the "first phase" of glucose-mediated insulin secretion by release of insulin from secretory granules in the β cell. Glucose entry into the β cell is sensed by glucokinase, which phosphorylates glucose to glucose-6-phosphate (G6P), generating ATP (17). Closure of K^+-ATP-dependent channels results in membrane depolarization and activation of voltage dependent calcium channels leading to an increase in intracellular calcium concentration; this triggers pulsatile insulin secretion (18). Augmentation of this response occurs by both a K+-ATP channel-independent Ca2+-dependent pathway and K+-ATP channel-independent Ca^{2+}-independent pathways of glucose action (19). Other mediators of insulin release include activation of phospholipases and protein kinase C (e.g. by acetycholine) and by stimulation of adenylyl cyclase activity and activation of β cell protein kinase A, which potentiates insulin secretion (19).

In healthy individuals, pancreatic secretion has biphasic pattern after glucose stimulation. Intravenous administration of glucose is associated with a rapid "first phase" of insulin release within 1 minute, peaking at 3-5 minutes, and lasting about 10 minutes; the slower onset "second phase" of insulin secretion begins shortly after the glucose bolus but is not apparent until 10 minutes later, lasts the duration of the hyperglycaemia and is to the glucose administration (20). The first phase of insulin secretion represents release of insulin already synthesized and stored in secretory granules; the second phase represents secretion of both stored and newly synthesized insulin. Overall insulin secretion relates to the total

dose of glucose and its rate of administration; maximal pancreatic response occurs with 20 g of glucose given intravenously over 3 minutes in humans (21). Insulin is the pivotal hormone regulating cellular energy supply and macronutrient balance, directing anabolic processes of the fed state (22). Insulin is essential for the intra-cellular transport of glucose into insulin-dependent tissues such as muscle and adipose tissue. Signaling abundance of exogenous energy, adipose tissue fat breakdown is suppressed and its synthesis promoted. In muscle cells, glucose entry enables glycogen to be synthesized and stored, and for carbohydrates, rather than fatty acids (or amino acids) to be utilized as the immediately available energy source for muscle contraction. Insulin therefore promotes glycogen and lipid synthesis in muscle cells, while suppressing lipolysis and gluconeogenesis from muscle amino acids. In the presence of an adequate supply of amino acids, insulin is anabolic in muscle (23).

Importantly, the normal pancreatic ß-cell can adapt to changes in insulin action - ie, a decrease in insulin action is accompanied by upregulation of insulin secretion and vice versa (2, 3, 9, 24). The curvilinear relation between normal ß -cell function and insulin sensitivity is illustrated in Figure 1.

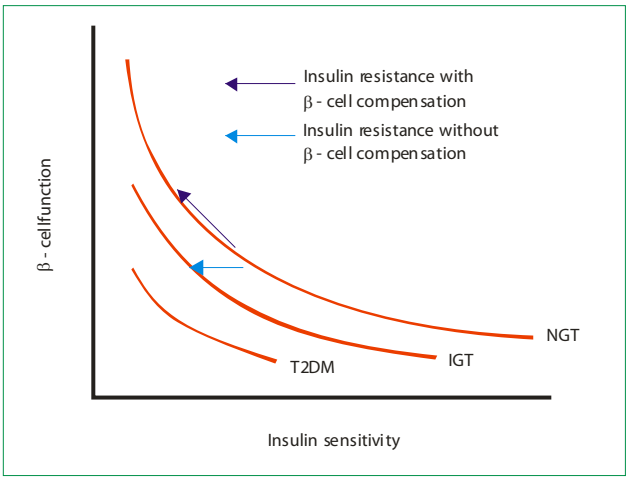


Figure 1. Hyperbolic relation between ß-cell function and insulin sensitivity. In people with normal glucose tolerance (NGT) a quasi-hyperbolic relation exists between ß-cell function

and insulin sensitivity. With deviation from this hyperbola, deterioration of glucose tolerance (impaired glucose tolerance [IGT] and type 2 diabetes occurs.

Deviation from this hyperbola, such as in patients with impaired glucose tolerance and type 2 diabetes in Figure 1, occurs when ß -cell function is inadequately low for a specific degree of insulin sensitivity. Thus, ß-cell dysfunction is a critical component in the pathogenesis of type 2 diabetes (25).

When insulin action decreases the system usually compensates by up-regulating ß-cell function. However, at the same time, concentrations of blood glucose at fasting and 2 h after glucose load will increase mildly (26). This increase may well be small, but over time becomes damaging because of glucose toxicity, and in itself a cause for ß-cell dysfunction. Thus, even with unlimited ß -cell reserve, insulin resistance paves the way for hyperglycaemia and type 2 diabetes (9).

1.3 Insulin resistance

Insulin is a peptide hormone secreted by the ß -cells of the pancreatic islets of Langerhans and maintains normal blood glucose levels by facilitating cellular glucose uptake, regulating carbohydrate, lipid and protein metabolism and promoting cell division and growth through its mitogenic effects (27).

Insulin resistance (IR) is a state in which a given concentration of insulin produces a less than normal biological response, and since one of insulin's major effects is to promote overall glucose metabolism, abnormalities of this action of insulin can lead to a number of important clinical and pathophysiological states (28-30). Insulin resistance can be due to three general categories or causes: (1) an abnormal ß-cell secretory product, (2) circulating insulin antagonists, or (3) a target tissue defect in insulin action (31). From the discussion of these mechanisms, it is apparent that insulin resistance can be categorized as the result of changes in insulin resistance, responsiveness, or both. Indeed, in vivo IR is usually defined as a decreased ability of a constant plasma insulin concentration to stimulate overall

glucose disposal under steady-state conditions where the hormonal effect has plateaued (32). Insulin resistance is characteristic feature of patients with impaired glucose tolerance (33, 34) and patients with NIDDM (34, 35, 36). Insulin resistance, as a prevalent medical condition, accompanies not only NIDDM, but also obesity, hypertension, metabolic syndrome and polycystic disease (37).

Insulin resistance is not a disease in itself, but a physiological abnormality that increases the likelihood that one or more of the abnormalities listed in Table 1 will be present.

Table 1. Abnormalities associated with insulin resistance/compensatory hyperinsulinemia

- Some degree of glucose intolerance
  - Impaired fasting glucose
  - Impaired glucose tolerance
- Dyslipidemia
  - ↑ Triglycerides
  - ↓ HDL-C
  - ↓ LDL-particle diameter (small, dense LDL particles)
  - ↑ Postprandial accumulation of triglyceride-rich lipoproteins
- Endothelial dysfunction
  - ↑ Mononuclear cell adhesion
  - ↑ Plasma concentration of cellular adhesion molecules
  - ↑ Plasma concentration of asymmetric dimethylarginine
  - ↓ Endothelial-dependent vasodilatation
- Procoagulant factors
  - ↑ Plasminogen activator inhibitor-1
  - ↑ Fibrinogen
- Hemodynamic changes
  - ↑ Sympathetic nervous system activity
  - ↑ Renal sodium retention
- Markers of inflammation
  - ↑ C-reactive protein, white blood cell count, etc.
- Abnormal uric acid metabolism
  - ↑ Plasma uric acid concentration
  - ↓ Renal uric acid clearance
- Increased testosterone secretion (ovary)
- Sleep-disordered breathing

HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein.

Furthermore, because these abnormalities occur more commonly in insulin-resistant individuals, these individuals are at increased risk to develop the clinical syndromes listed in Table 2.

Table 2. Clinical syndromes associated with insulin resistance

- Type 2 diabetes
- Cardiovascular disease
- Essential hypertension
- Polycystic ovary syndrome
- Nonalcoholic fatty liver disease
- Certain forms of cancer
- Sleep apnea

Patients with impaired glucose tolerance have relatively mild IR, whereas patients with NIDDM have more severe IR (33, 34). The frequency of the IR increases with the worsening of the degree of carbohydrate intolerance (34). Thus, most of patients with impaired glucose tolerance are insulin resistant, while essentially every NIDDM patient with significant fasting hyperglycemia displays this abnormality. Obesity is a well-known condition which also leads to the development of IR. Since most of NIDDM patients are overweight, obesity-induced IR is thought to be a contributing factor in the hyperglycemia of these patients. However, obesity does not account for all of the IR in this type of diabetic patients, since the IR exceeds that caused by obesity alone, and non-obese patients with NIDDM are also insulin-resistant (33, 38, 39).

1.4. Diabetic cardiomyopathy

Diabetes mellitus, both insulin-dependent and non-insulin-dependent, is a major independent risk factor for coronary artery disease (CAD). The patients with type 2 diabetes usually have many genetically interlinked risk factors for coronary atherosclerosis, such as arterial hypertension, dyslipidaemia, android obesity and hyperinsulinaemia with insulin resistance (26, 37). It is suggested that each of these is a risk factor for diastolic dysfunction (40). Subjects with type 2 diabetes have a two- to four- fold higher risk of CAD than non-diabetic subjects of the same age (41). Diastolic heart failure has been introduced as a separate clinical entity estimated to be responsible for approximately 1/3 of all cases with heart failure (42, 43).

Over the last three decades, a number of epidemiological, autopsy, animal, and clinical studies have proposed the presence of diabetic heart disease as a distinct clinical entity (44-46). "Diabetic cardiomyopathy" as an entity was originally described in 1972 on the basis of observations in four diabetic patients who presented with heart failure without evidence of hypertension, CAD, valvular or congenital heart disease (46). The increasing recognition of this additional cardiac pathology is supported by data from epidemiological, molecular and more refined diagnostic studies. The Framingham study demonstrated the increased incidence of congestive heart failure in diabetic males (2.4:1) and females (5:1) independent of age, hypertension, obesity, CAD and hyperlipidaemia (47). Other prospective studies also showed that diabetic patients have a significantly increased lifetime risk of developing heart failure (48), and increased mortality from both Q-wave and non-Q-wave myocardial infarction (49,50). The previous studies have shown a link between dilated cardiomyopathy and diabetes (51). This finding suggests that there is an additional pathological process to diabetic myocardium which predisposes it to more extensive damage and subsequent failure (52).

Diabetic cardiomyopathy has been proposed as an independent cardiovascular disease. The development of diabetic cardiomyopathy is likely to be multifactorial. Alleged mechanisms include metabolic disturbances, myocardial fibrosis, small vessel disease,

autonomic dysfunction, and insulin resistance (53). However, the exact causes and mechanisms of diabetic cardiomyopathy still remain unclear (46, 54, 55).

1.5. Left ventricular diastolic dysfunction

Diastolic heart failure is a clinical syndrome characterized by the symptoms and signs of heart failure, a preserved ejection fraction, and abnormal diastolic function. From a conceptual perspective, diastolic heart failure occurs when the ventricular chamber is unable to accept an adequate volume of blood during the diastole, at normal diastolic pressures and at volumes sufficient to maintain an appropriate stroke volume (56). Diastole encompasses the time period during which the myocardium loses its ability to generate force and shorten and returns to an unstressed length and force. By extension, diastolic dysfunction occurs when these processes are prolonged, slowed, or incomplete (56). The measurements that reflect changes in this normal diastolic function generally depend on the onset, rate, and extent of ventricular pressure decline and the relationship between pressure and volume or stress and strain during diastole (56, 57, 58). The responsible mechanisms for the diastolic function abnormalities that cause the development of diastolic heart failure can be divided into intrinsic (myocardial) and extrinsic factors of the myocardium (extramyocardial) as are shown in Table 3 (59).

Table 3. Diastolic Heart Failure Mechanisms

Extramyocardial
- *Haemodynamic load: early diastolic load, afterload*
- *Heterogenity*
- *Pericardium*

Myocardial
- *Cardiomyocite*
  - Calcium homeostasis
    - Calcium concentration
    - Sarcolemal and SR calcium transport function
    - Modifying proteins (phosphalamban, calmodulin, calsequestran)
  - Myofilaments
    - Tn-C calcium binding
    - Tn-I phospholiration
    - Myofilament calcium sensitivity
    - α/ß myosin heavy chain ATPase ratio
  - Energetics
    - ADP/ATP ratio
    - ADP and Pi concentration
  - Cytoskeleton
    - Microtubules
    - Intermediate filaments (desmin)
    - Microfilaments (actin)
    - Endosarcomeric skeleton (titin, nebulin)
- *Extracellular matrix*
  - Fibrillar collagen
  - Basement membrane proteins
  - Proteglycans
  - MMP/TIMP
- *Neurohormonal activation*
  - Renin-angiotensin-aldosteron
  - Sympathetic nervous system
  - Endothelin
  - Nitric oxide
  - Natriuretic peptides

Abbreviations: MMP-matrix metalloproteinase; TIMP-tissue inhibitor of matrix metalloproteinase; SR-sarcoplasmic reticulum; Tn-C – troponin C; Tn-I – troponin I;

The changes in the cardiac muscle cells themselves can cause diastolic dysfunction. These include the changes in calcium homeostasis, which can result in increased cytosolic calcium concentration, prolongation of the calcium transient, and delayed and slowed diastolic decline in cytosolic calcium concentration. These changes have been shown to occur in cardiac disease and cause abnormalities in both active relaxation and passive stiffness (60). Modification of any of the steps during relaxation in the myofilament contractile proteins, or the ATPase that that catalyzes them, can alter diastolic function (61, 62). Changes in some of the cytoskeletal proteins (desmin, actin, titin, nebulin, α-actinin, myomesin, and M-protein), have been shown to alter diastolic function, too (63, 64, 65). Previous studies have shown that a chronic alteration in collagen metabolism result in alteration of diastolic function (66, 67). Neurohumoral and cardiac endothelial activation and/or inhibition have shown to alter diastolic function. Acute activation or inhibition of neurohumoral and cardiac endothelial systems has been shown to alter relaxation and stiffness (68). Chronic activation of renin-angiotensin-aldosterone system has been shown to increase fibrillar collagen of the extracellular matrix and to be associated with increased stiffness (59).

The noninvasive assessment of diastolic dysfunction mainly relies on Doppler studies of transmitral inflow, measuring mitral inflow velocities, deceleration time, isovolumic relaxation time, and assessing flow patterns (Fig. 2).

As diastolic function worsens, early diastolic LV filling (E wave) is reduced, and the patient demonstrates a delayed relaxation pattern. However, as left atrial pressure increases, the E wave returns to normal, producing a mitral pattern indistinguishable from normal (pseudonormal), until the development of a restrictive filling pattern, which reflects a high left atrial pressure, usually to the extent that symptoms of left heart failure appear.

The preload dependence of these techniques means that measurements in the same patient may change from one category to the next as left atrial pressure is increased or decreased (69).

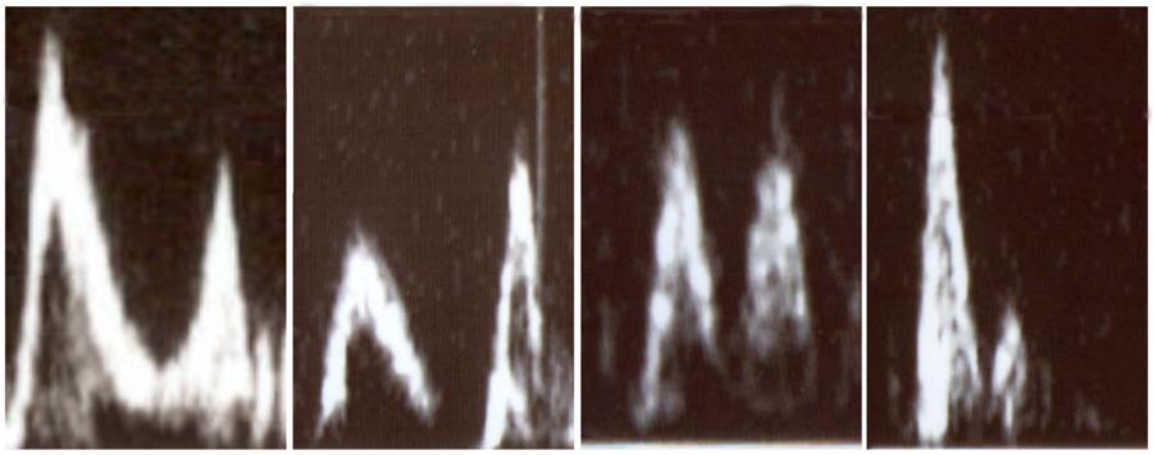


Fig. 2. Left ventricular filling patterns derived from assessment of transmitral flow. Worsening of LV function leads initially to delayed relaxation, characterized by reduction of the E wave and prolongation of the deceleration time (*horizontal vector or diagonal* marked on each frame). The process is reversed by elevation of LV filling pressure increasing E wave velocity and shortening deceleration time pseudonormal and restrictive).

Tissue Doppler imaging, which uses Doppler to quantify the velocity of tissue rather thanblood, has been available as a clinical tool for over a decade (70). Early diastolic mitral annular velocity (E') measured by Doppler tissue imaging has been reported to be a preload independent index of myocardial relaxation (71), and LV filling pressures can be estimated by combining mitral inflow (early filling [E]) and E' (72). The tissue Doppler imaging appears to be much less influenced by preload in an impaired ventricle, and does not pseudonormalise in the same way as the transmitral flow (73).

1.6. Diastolic dysfunction in diabetic patients

Changes in diastolic function are a widely reported finding in diabetic animals (74, 75) and diabetic patients without evidence of heart disease caused by other factors (76-87). In experimental diabetes, papillary muscles from animal hearts have shown prolongation of relaxation and considerable slowing in relaxation velocity (88, 89), and isolated perfused

hearts from type II diabetic rats showed prolonged isovolumic relaxation time and increases in late mitral inflow velocity and LV end-diastolic pressure (90). Diastolic function parameters in diabetic patients are analogous to those in animal studies. Diastolic inflow patterns are frequently abnormal, reflecting underlying abnormalities in relaxation and/or reduced myocardial compliance. LV diastolic dysfunction appears to be quite common in well-controlled type II diabetic patients without clinically detectable heart disease (54, 86, 87, 91-95).

Several studies have examined the clinical correlates of diastolic function changes in diabetes. In a study, which included diabetic patients without known heart disease, these abnormalities were unrelated to sex, age, duration of diabetes, or the presence or extent of complications (54).

Studies that have examined both systolic and diastolic dysfunction in both type I and type II diabetes suggest that the latter is more susceptible to preclinical changes. In a study, including patients with type I and type II diabetes, without hypertension and coronary artery disease, the ratio of mitral early peak diastolic velocity and late peak velocity were more severely decreased in type II than type I diabetics (96). These findings have been confirmed in a subsequent study, in which ventricular filling was impaired more significantly in the type II diabetic patients than in the type I diabetic patients, especially the peak early filling velocity E (97). However, not all studies show the presence of diastolic dysfunction in diabetic patients (98, 99).

1.7. Insulin resistance and diastolic dysfunction

Insulin resistance (IR) is a characteristic feature of human obesity and type 2 diabetes. The close association between IR and obesity has made it difficult to establish whether IR *per se* is independently associated with various components of the cardiovascular dysmetabolic syndrome (100). Insulin resistance is associated with hypertension (101), coronary artery disease (102, 102), and diabetes (104, 105).

Previous studies, however, have suggested that IR might be an independent cardiovascular risk factor in non-diabetic subjects (106, 107) and in patients with type 2 diabetes (108). Greater left ventricular mass and reduced arterial compliance are reported to be associated with insulin resistance (109). The increase in left ventricular ejection fraction by insulin infusion after submaximal exercise has been reported to be lower in diabetic patients than in healthy subjects, a finding that could be explained by IR (110). No significant differences regarding the diastolic volumes and mean blood pressure were reported in this study (110). Insulin resistance has been linked to LV early diastolic abnormalities in hypertension, independently from the influence exerted by increased blood pressure levels, overweight, and LV hypertrophy (111, 112). Moreover, Nagano et al. found no correlation between left ventricular systolic and diastolic parameters and IR in hypertensive patients (113). Other investigators have reported an independent association between IR and carotid intima-medial thickness (an early indicator of atherosclerosis) among hypertensive patients (114, 115) and normotensive pre-menopausal women (116). Therefore, the role of IR in cardiovascular diseases deserves further investigation.

2. AIMS OF THE STUDY

The main objective of this thesis is to explore whether there is an association between IR and left ventricular diastolic dysfunction in patients with impaired glucose tolerance (IGT) and type 2 diabetes mellitus. Well-accepted laboratory and echocardiographic criteria were used to estimate IR and left ventricular diastolic function. We aimed at selecting a group of patients with IGT or diabetes with minimal confounding factors that may interfere with the diastolic function of the left ventricle. Given the confounding effect of arterial hypertension and ischaemic heart disease which have a disproportionately high incidence in patients with diabetes compared with subjects without diabetes and which interfere (are determinant of) with left ventricular diastolic function patients with these morbid conditions were excluded from the study.

3. METHODS

3.1. Patients

A total of 119 subjects without clinical evidence for cardiovascular diseases were enrolled in our study. Based on the World Health Organization (WHO) criteria (117) for diagnosis of diabetes using fasting plasma glucose (FPG) and 120 min plasma glucose, subjects were divided into 3 groups: 1) Subjects with normal glucose tolerance (NGT), defined as fasting plasma glucose < 7.0 mmol/L and 120 min plasma glucose < 7.8 mmol/L; 2) Subjects with IGT, defined as fasting plasma glucose between < 7.0 mmol/ and 120 min plasma glucose between ≥ 7.8 mmol/ and <11.1 mmol/L; 3) Patients with diabetes were defined by fasting plasma glucose ≥7.0 mmol/L and 120 min plasma glucose ≥11.1 mmol/L. In patients known to have diabetes, the diagnosis was based on the previous history of diabetes and 120 min PG ≥ 11.1 mmol/L. The subjects of all groups were matched for age and sex. At the time of inclusion in the study 42 patients were known as diabetic patients. They were under treatment with glibenclamide (18 patients), gliclazide

(11 patients) and diet (13 patients). The remaining 28 patients diagnosed with diabetes at the time of inclusion in the study and subjects with NGT and IGT were not on drug therapy.

Insulin resistance was assessed using Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and Quantitative Insulin Sensitivity Check Index (QUICKI) (118, 119).

Exclusion criteria were: arterial hypertension, ischemic heart disease (detected by meticulous anamnesis, surface electrocardiogram, exercise testing and presence of left ventricular wall abnormalities in echocardiographic examination), cardiac arrhythmias, congenital or acquired valvular heart disease, infiltrative heart disease, pericardial disease, chronic renal failure and pregnancy, age greater than 75 years, insulin therapy and subjects with poor echocardiographic window. All subjects and patients were examined and included in the study during the same time period. All subjects gave informed consent for participation in the study. The study protocol conformed to the Declaration of Helsinki. The study protocol was presented, revised and accepted by ethics committee of the Internal Medicine Clinic of University Clinical Center of Kosova, in Prishtina, Kosovo.

3.2. Data collection

In all subjects included in the study, the weight, height, waist and hip were measured with subjects wearing light clothing without shoes, and body-mass index (BMI) waist-to-hip ratio were calculated. In patients with diabetes, the information on the duration of diabetes and current medical treatment was carefully collected. Routine biochemical measurements were performed including lipid profile (total cholesterol, high density lipoproteins [HDL], low density lipoproteins [LDL], very low density lipoproteins [VLDL] and triglycerides), as well as serum creatinine and urea.

A standard (75 g) 2 hours oral glucose tolerance test (OGTT) was performed in all subjects. In diabetic patients hypoglycemic agents were stopped 3 days before OGTT. All subjects consumed a diet containing at least 200 g carbohydrate for 3 days before the test. After overnight fasting, the 75 g glucose was given orally within 5 minutes. Blood samples for the determination of plasma glucose and insulin were drawn at 0, 10, 20, 30, 60 and 120

min after intake of glucose. Serum glucose was measured by the glucose oxidase GOD-PAP method. Insulin was determined by radioimmunoassay (RIA) method using a commercially available kit.

Insulin resistance was assessed by using Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and Quantitative Insulin Sensitivity Check Index (QUICKI). The HOMA-IR was calculated with formula HOMA-IR = $glucose_0$ (in mmol/L) x $insulin_0$ (in μU/mL) / 22.5 (118). QUICKI was calculated with formula QUICKI =1/[log($insulin_0$) + log($glucose_0$)] (insulin in mU/mL, glucose in mg/dL) (119).

3.3. Echocardiographic examinations

All patients underwent echocardiographic examination with echocardiographic machine equipped with multi-frequency probes from 2.5 - 5 MHz (Agilent Image-Point, Hewlett Packard). Echocardiographic examination was performed using standard views. Diastolic function of the left ventricle was assessed by pulsed Doppler. The pulsed Doppler sample volume was positioned at the tips of the mitral leaflets. We registered the maximal early filling velocity (E wave), maximal late (atrial) filling velocity (A wave), from which the E/A ratio was derived, and the deceleration time of E wave (DT-E). An E/A ratio < 1 was considered as a criterion for diastolic dysfunction of the left ventricle (LV). Echocardiographical examinations were performed by operators unaware of the presence of diabetes or IR status. All patients and healthy subjects underwent stress test ergometry in the period of less than a week from the echocardiographic examination.

3.4. Statistical analysis

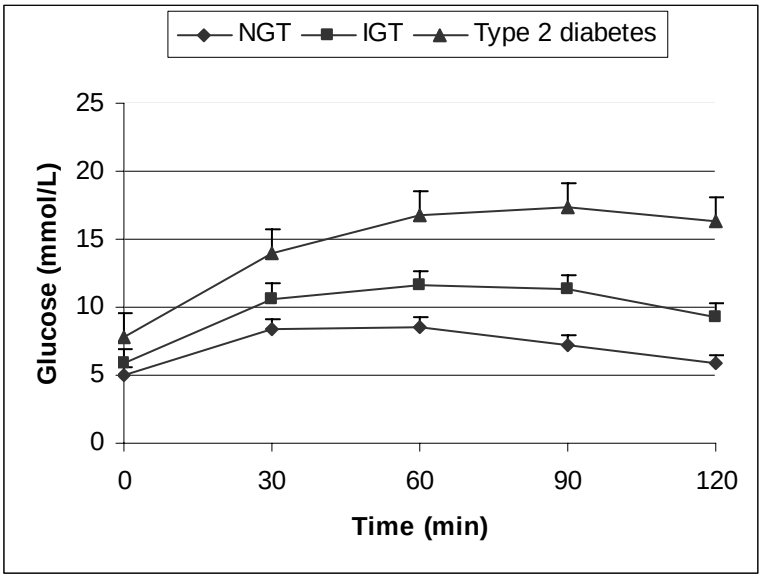
Data are expressed as mean ± SD or mean ± SEM for continuous variables and as percentages for discrete variables. Continuous variables were compared with Kruskal-Wallis test. Discrete variables were compared with chi-square test. Multiple linear regression analysis was used to identify the independent correlates of diastolic dysfunction (E/A ratio). Differences were considered to be statistically significant for P values <0.05.

4. RESULTS

4.1. Baseline Data

There were 29 subjects with NGT, 20 subjects with IGT and 70 patients with diabetes. Twenty-eight of the patients with diabetes were detected by OGTT whereas 42 patients were known diabetic patients. Duration of diabetes in these patients was 4.1 ± 4.4 years. Plasma glucose and insulin response to OGTT are shown in Figure 3.

Baseline clinical and laboratory data are shown in Table 4. The majority of demographic and clinical data did not show significant differences among patients in different groups. Significant differences were observed regarding fasting plasma glucose, 2-hour plasma glucose as well as 2 models used to assess the IR (HOMA-IR and QUICKI; Table 4).



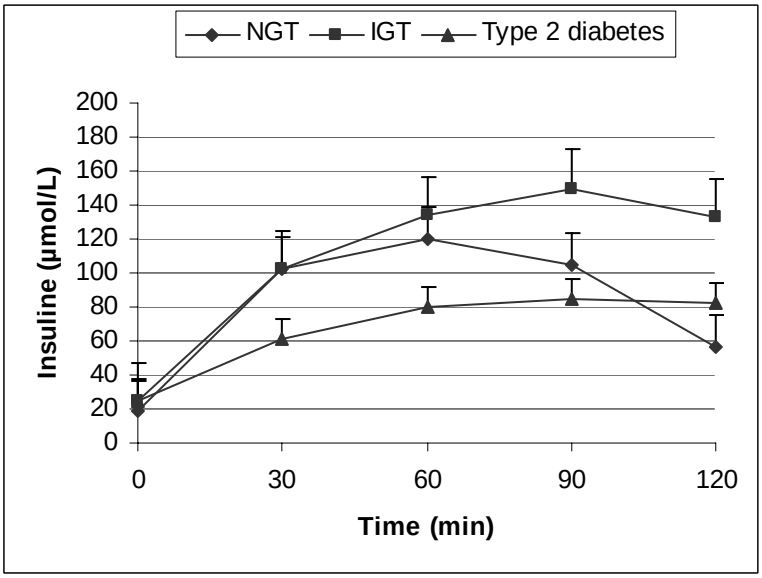


Figure 3. Plasma Glucose (Upper panel) and Insulin levels (lower panel) during OGTT in Subjects with Normal Glucose Tolerance (NGT), Impaired Glucose Tolerance (IGT) and Type 2 Diabetes. Data are mean ± SEM.

Table 4. Clinical and Laboratory Data

Variable	NGT (n=29)	IGT (n=20)	Type 2 diabetes (n=70)	*P*
Gender (male)	8	6	19	0.969
Age (years)	52.00±6.07	54.65±6.69	54.61±6.54	0.086
Weight (kg)	84.90±19.06	86.40±12.52	80.89±12.32	0.233
Height (cm)	164.69±12.55	161.88±6.52	161.57±8.91	0.796
BMI (kg/cm^2)	31.26±6.99	32.91±4.90	30.30±6.20	0.278
Waist perimeter (cm)	101.17±18.22	101.45±9.16	100.43±11.77	0.723
Hip perimeter (cm)	111.10±18.18	107.45±8.38	107.15±9.39	0.071
Waist/hips ratio	0.92±0.13	0.94±0.05	0.93±0.08	0.722
Systolic BP	127±10	131±9	129±11	0.103
Diastolic BP	86±7	86±8	87±10	0.251
Urea (mmol/L)	5.64±1.62	5.72±1.39	5.74±1.60	0.944
Creatinine (μmol/L)	69.93±14.99	72.55±13.50	74.20±15.52	0.299
Triglycerides (mmol/L)	1.96±1.27	1.69±0.42	2.11±1.99	0.235
Total cholesterol (mmol/L)	4.81±1.51	4.90±1.12	5.20±1.61	0.557
HDL (mmol/L)	1.36±0.63	1.24±0.22	1.22±0.47	0.140
LDL (mmol/L)	2.57±0.98	2.90±1.13	2.83±1.88	0.408
VLDL (mmol/L)	0.87±0.59	0.76±0.30	0.90±0.61	0.988
FPG (mmol/L)	4.95±0.64	5.88±1.15	7.80±0.88	<0.001
2-hr PG	5.81±1.06	9.24±1.05	16.28±2.95	<0.001
Fasting insulin (μmol/L)	18.64±7.51	24.76±15.32	25.15±17.98	0.427
HOMA-IR	4.20±1.20	6.45±3.83	8.70±6.26	<0.001
QUICKI	0.54±0.11	0.49±0.08	0.47±0.08	<0.001

Data are number of patients or mean ± SD

Abbreviations: NGT-normal glucose tolerance; IGT-impaired glucose tolerance; BMI-body/mass index; SBP-systolic blood pressure; DBP-diastolic blood pressure; HDL – high density lipoproteins; LDL – low density lipoproteins; VLDL – very low density lipoproteins; FPG-fasting plasma glucose; 2-hr PG – 2 hr postprandial glucose; HOMA-IR – homeostasis model assessment of insulin resistance; QUICKI – quantitative insulin sensitivity check index.

4.2. Echocardiograhic Data

Echocardiographic data are shown in Table 5. There were not significant differences between the groups regarding left ventricular end-diastolic and end-systolic dimension, left ventricular fractional shortening and ejection fraction, thickness of interventricular septum and posterior wall, left atrium and aorta. Significant differences between groups regarding the pulsed Doppler transmitral variables: E wave (0.72±0.16 m/s in the group with NGT, 0.62±0.13 m/s in the group with IGT and 0.58±0.17 m/s in the group with diabetes; $p<0.001$); A wave (0.61±0.13 m/s in the group with NGT, 0.62±0.11 m/s in the group with IGT and 0.71±0.14 m/s in the group with diabetes; $p=0.006$) and E/A ratio (1.22±0.33 in the group with NGT, 1.02±0.24 in the group with IGT and 0.85±0.26 in the group with diabetes; $p<0.001$, Table 4). The proportion of patients with a ratio E/A<1 was 27.6% (8 of 29 subjects with NGT), 55% (11 of 20 subjects with IGT) and 75.7% (53 of 70 patients with diabetes) ($P<0.001$). Deceleration time of E wave did not differ significantly between groups. The E/A ratio, an index of diastolic function, correlated with indexes of IR: HOMA-IR ($r = -0.30$, $P=0.001$) and QUICKI ($r=0.37$, $p<0.001$; Figure 4).

Table 5. Echocardiographic Data

Variable	NGT (n=29)	IGT (n=20)	Type 2 diabetes (n=70)	*P*
LV end-diastolic dimension (cm)	5.26±0.48	5.23±0.43	5.12±0.46	0.251
LV end-systolic dimension (cm)	3.59±0.54	3.53±0.29	3.45±0.49	0.251
Fractional shortening (%)	33.9±4.93	32.5±3.75	32.6±5.66	0.383
Ejection fraction (%)	68.28±7.37	66.60±7.42	64.84±9.13	0.181
Interventricular septum (cm)	0.93±0.11	10.05±0.09	9.54±0.10	0.908
Posterior wall of LV(cm)	0.86±0.10	0.91±0.10	0.89±0.11	0.330
Left atrium (cm)	3.84±0.34	3.82±0.32	3.77±0.32	0.602
Aorta (cm)	3.12±0.39	3.33±0.26	3.16±0.34	0.057
E (m/s)	0.72±0.16	0.62±0.13	0.58±0.17	<0.001
A (m/s)	0.61±0.13	0.62±0.11	0.71±0.14	0.006
E/A	1.22±0.33	1.02±0.24	0.85±0.26	<0.001
E/A ratio <1	8 (27.6%)	11 (55%)	53(75.7%)	<0.001
DT-E (ms)	161.49±29.6	151.33±18.4	148.22±31.7	0.217

Data are mean ± SD

Abbreviations: NGT-normal glucose tolerance; IGT-impaired glucose tolerance; LV – left ventricle; DT – deceleration time.

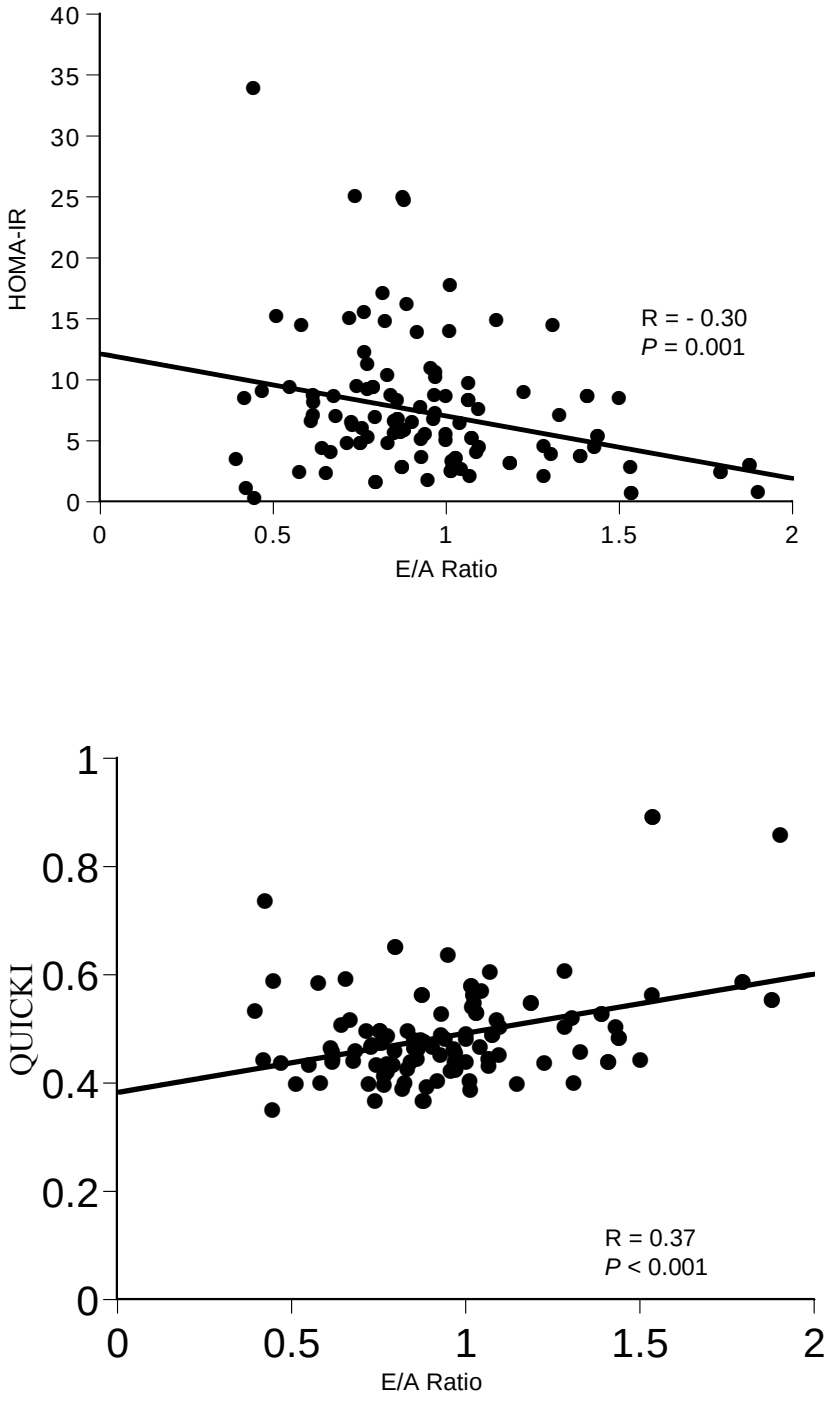


Figure 4. Correlations between E/A ratio and indexes of IR HOMA-IR (upper panel) and QUICKI (lower panel).

Multiple linear regression model was used to identify the independent correlates of diastolic dysfunction (E/A ratio). The following variables were entered into the model: age, sex, body-mass index, waist-to-hip ratio, QUCKI, creatinine, low density lipoprotein level, triglyceride level, high density lipoprotein level, fasting glucose, 2-hour glucose, basal insulin level, interventricular septum thickness, left ventricular posterior wall thickness, left ventricular ejection fraction and left atrial dimension. The dependent variable (E/A ratio) was entered into the model as a continuous variable. The model showed that age ($P<0.001$), triglyceride level ($P=0.01$), low density lipoprotein level ($P=0.01$) 2-hour glucose ($P=0.01$) and QUICKI ($P=0.034$) correlated independently with the E/A ratio (index of diastolic function). The overall R^2 of the model was 0.48.

5. DISCUSSION

Clinically, left ventricular dysfunction associated with diabetes in the absence of other predisposing factors has been termed diabetic cardiomyopathy. Diabetic cardiomyopathy was described in diabetic patients who had no evidence of coronary artery disease, arterial hypertension or valvular heart disease (26, 55, 120-122). Clinical evidence of left ventricular involvement in patients with diabetes including left ventricular systolic and diastolic dysfunction has been noted in patients with insulin-dependent diabetes mellitus and to a lesser degree in patients with non-insulin-dependent diabetes. Abnormal systolic function has been evidenced by various parameters or tests including abnormal left ventricular ejection fraction (123), abnormal stroke volume (124), response to exercise (125) and abnormal systolic time intervals (126). On the other hand, diastolic inflow patterns in diabetic patients are frequently abnormal, reflecting underlying abnormalities in relaxation and/or reduced myocardial compliance. Diastolic left ventricular dysfunction has been evidenced by prolongation of the isovolumic relaxation period (127), rapid filling period (128) and reduced extent of early diastolic filling (129, 130). A general consensus is that diastolic dysfunction may be evidenced early in the course of the disease and earlier than systolic dysfunction. The exact causes of the occurrence of heart failure in diabetic patients remain unclear (55, 131, 132). However, numerous pathological findings such as myocardial hypertrophy, circumvented areas of perivascular and interstitial fibrosis, endothelial proliferation, narrowing and distortions of small arterioles and capillary microaneurisms, deposition of glycoprotein materials in interstitium have been reported in patients with diabetes and congestive heart failure with no evidence of arterial hypertension or coronary artery disease (133-135) The incidence of heart failure in patients with non-insulin dependent diabetes is higher than in control subjects, and diastolic heart failure seems to be one of its main causes (136-138). Previous studies yielded conflicting results regarding the prevalence of left ventricle functional abnormalities (systolic and diastolic dysfunction) in asymptomatic patients with non-insulin dependent diabetes (87, 106, 108, 117, 139, 140). It is widely accepted, however, that diastolic dysfunction is the most

prominent defect associated with diabetic cardiomyopathy. Numerous cellular and molecular mechanisms linking diabetic status with left ventricular diastolic dysfunction have been proposed. A major factor for the high prevalence of diastolic dysfunction in patients with diabetes is myocardial fibrosis. As the Strong Heart Study has reported, there is a close relationship between frequency of left ventricular diastolic dysfunction and level of HbA1c (141, 142). Advanced glycosylation end products (AGEs) are often implicated as factors that promote myocardial stiffness and reduced diastolic function in diabetic patients (143). Accumulation of AGEs in the myocardium of diabetic patients results in endothelial basement membrane damage via increased expression of their receptor and increased production of collagen and increased cross linking of collagen and myocardial fibrosis and diastolic dysfunction (144). Intracellular myocardial glycation alters calcium homeostasis leading to slowed cytoplasmic calcium removal and slowed myocyte relengthning and diastolic dysfunction (145, 146). In a previous study, we have shown that in patients with non-insulin dependent diabetes mellitus without evidence of structural heart disease or arterial hypertension, diastolic LV dysfunction is a frequent finding in nearly two thirds of the patients (65.8%) and non-insulin dependent diabetes mellitus is an independent correlate of left ventricular diastolic dysfunction (87). Furthermore, in this study we observed the existence of an inverse correlation between duration of the diabetes and the magnitude of E/A ratio, an index of left ventricular diastolic function (87).

Echocardiographic examination has made it easier to detect initial abnormalities in the left ventricular diastolic dysfunction before their clinical appearance. Doppler echocardiography has become a well-accepted, reliable noninvasive tool to study the left ventricular diastolic dysfunction. In this study, we used Doppler echocardiography to assess the left ventricular diastolic function and correlated these findings with IR estimated by HOMA-IR and QUICKI indexes.

The current study offers solid evidence on the existence of a close relationship between IR and left ventricular diastolic dysfunction. The principal finding of the present study was that IR is an independent correlate of left ventricular diastolic dysfunction in subjects with IGT and patients with type 2 diabetes without arterial hypertension. The association between IR and diastolic dysfunction of the left ventricle was observed, both in

univariate and after adjustment in the multivariate model. A significantly greater proportion of subjects/patients with echocardiographic evidence of left ventricular diastolic dysfunction were observed in subject with IGT and patients with diabetes compared with subjects with NGT. Specifically, a progressive decrease in the magnitude of E /A ratio and a progressive increase in the proportion of patients with an E / A ratio < 1 were observed from subjects with normal glucose tolerance to subjects with impaired glucose tolerance and to patients with diabetes. Furthermore, both HOMA-IR and QUICKI become gradually more indicative of IR from subjects with normal glucose tolerance to those with impaired glucose tolerance and patients with diabetes. We found a good correlation between indexes of IR and diastolic dysfunction of the left ventricle. To our knowledge this is the first study to have reported such an association in a population of predominantly diabetic patients. In multivariate analysis IR was an independent correlate of left ventricular diastolic dysfunction even after adjustment for potentially confounding variables including obesity assessed by body-mass index and waist-to-hip ratio. This finding is of special importance particularly when the intricate relationship between IR and obesity is considered (106). On the other hand patients with arterial hypertension, another frequent associate of diabetes and obesity, are not included in this study so that the potential confounding effect of arterial hypertension in the left ventricular diastolic function has been eliminated. Although, from clinical point of view, arterial hypertension is a frequent associate of diabetes with intricate links between them and a contributor to left ventricular diastolic dysfunction, the exclusion of patients with arterial hypertension is important in a sense that we avoided the confounding effects of co-existent arterial hypertension on left ventricular diastolic function. Arterial hypertension *per se* promotes or exacerbates cardiac dysfunction seen in patients with diabetes through left ventricular hypertrophy and metabolic dysfunction. Thus our data demonstrate that in a group of patients without arterial hypertension, IR *per se* is associated with impaired left ventricular diastolic function. Regarding the relationship between systolic and diastolic dysfunction we found that diabetic patients without arterial hypertension or clinical evidence of structural heart disease have reduced left ventricular diastolic function in the presence of preserved systolic function of the left ventricle (42, 107, 108, 140). Thus our study confirms that isolated diastolic dysfunction (without

echocardiographic evidence of left ventricular systolic dysfunction) may be found in patients with diabetes. Our findings are consistent with and corroborate those studies that have suggested that the impairment of left ventricular diastolic function in patients with diabetes occurs earlier than the impairment of left ventricular systolic function.

The finding of a close association between IR and the impaired left ventricular diastolic function seems to be clinically relevant. A recent population-based study in subjects free of congestive heart failure at the time of recruitment for the study has unequivocally proven that IR predicts the development of congestive heart failure independent of traditional risk factors including diabetes mellitus (147). Furthermore this study suggested that previously described association between obesity and congestive heart failure in fact may be mediated largely by IR (147). A numerous mechanisms through which IR could promote congestive heart failure, among them, accumulation of AGEs and increased collagen-cross linking and myocardial stiffness and diastolic heart failure (148, 149), growth factor properties of insulin leading to increased myocardial mass (150), increased sodium leading to decompensation in subjects with subclinical congestive heart failure (151), increased sympathetic activation (152) and increased sensitivity to angiotensin II (153) leading to myocardial hyperthrophy and fibrosis have been proposed (147).

5.1. Mechanisms of Association between Insulin resistance and Diastolic Dysfunction

The exact mechanisms that explain the association between IR and diastolic dysfunction of the left ventricle have not been fully elucidated. Earlier in this section the importance of AGEs in the increased cross-linking between collagen molecules leading to myocardial stiffness with potential consequence impaired diastolic lengthening of myocardial fibers has been discussed. Increased myocardial fibrosis is a widely accepted contributor to diastolic dysfunction in patients with diabetes. It is well known that impaired relaxation is one of the earliest manifestations of cardiac involvement in various diseases. A recent experimental study demonstrated that metabolic abnormalities in the pre-stage of type 2 diabetes result in left ventricular fibrosis (154). Additionally, this study

demonstrated increased levels of transforming growth factor beta-1 (TGF-ß1) receptor in the rat left ventricular myocytes and suggested that metabolic abnormalities including hyperglycemia, hyperinsulinemia and IR may be involved in the onset of cardiac fibrosis (154). Other studies have demonstrated that insulin exerts a growth-stimulating effect on cardiac myocytes and increases collagen production from fibroblasts (155, 156). Another potential factor that may impair left ventricular filling is impairment in the calcium homeostasis by hyperinsulinemia due to IR leading to delayed cytoplasmic removal of calcium which may lead to prolonged action potential duration and impairment of early left ventricular filling (153). In fact this could be one of the earliest manifestations of the IR with an impact on the left ventricular diastolic dysfunction. In the real life conditions of patients with diabetes, the presence of arterial hypertension and coronary artery disease are important factors leading to, or exacerbating the impairment of, diastolic function. Although these mechanisms may point to the involvement of IR in the genesis of diastolic dysfunction, full explanation of the mechanisms through which IR promotes left ventricular diastolic dysfunction remains largely unknown.

5.2. Limitations of the Study

This study has some limitations. Coronary angiography was not performed in patients included in this study. Instead, coronary artery disease was excluded based on the lack of anamnestic and clinical data including surface electrocardiogram and absent regional abnormalities in the echocardiogram as well as negative exercise testing. However, latent subclinical coronary atherosclerosis could not be entirely ruled out. However, we do not believe that subtle coronary atherosclerosis without clinical manifestations including exercise-induced myocardial ischemia could have impacted the findings of this study to any considerable degree. The proportion of female patients in this study was uncommonly high. An important factor that resulted in such a high proportion of female patients in this study is related to exclusion of patients with ischemic heart disease who were mostly men. Tissue Doppler may be another accurate method of assessing left ventricular function, particularly in the presence of pseudonormalization of the left ventricular diastolic function. By

exclusion of patients with coronary artery disease and arterial hypertension we supposed that conditions for pseudonormalization were markedly reduced. In this situation conventional transmitral pulsed-Doppler accurately assesses the left ventricular diastolic function. Glucosylated hemoglobin (HbA1c), a marker of metabolic control was not available to all of the patients of our study. Thus a relationship between the metabolic control as reflected by HbA1c level and left ventricular diastolic function could not be assessed by the present study. Finally, although IR was shown to be an independent correlate of left ventricular diastolic dysfunction in asymptomatic patients, the information regarding the influence IR on the future development of congestive heart failure or coronary artery disease cannot be provided by this study.

6. CONCLUSIONS

This study confirmed the existence of a close association between insulin resistance and impaired left ventricular diastolic function. Specifically, in asymptomatic non-hypertensive subjects with impaired glucose tolerance and in non-hypertensive patients with diabetes and no clinical evidence for ischemic heart disease, insulin resistance was found to be independently associated with impaired diastolic function of the left ventricle. Future studies are needed to investigate mechanisms by which insulin resistance leads to impairment in the diastolic function of the left ventricle.

7. SUMMARY

Aim: The aim of this study was to explore the relationship between insulin resistance (IR) and the left ventricular diastolic function in patients with type 2 diabetes and subjects with impaired glucose tolerance (IGT).

Methods: The study included 119 subjects who underwent oral glucose tolerance test (OGTT). Insulin resistance was assessed using Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and Quantitative Insulin Sensitivity Check Index (QUICKI). Left ventricular diastolic function was assessed using trans-thoracic Doppler echocardiography.

Results: Based on the OGTT results, 29 subjects had normal glucose tolerance (NGT), 20 subjects had impaired glucose tolerance (IGT), and 70 patients had type 2 diabetes. There were significant differences among the patients in groups with NGT, IGT and diabetes regarding HOMA-IR (4.20±1.20 vs. 6.45±3.83 vs. 8.70±6.26; P<0.001) and QUICKI (0.54±0.11 vs. 0.49±0.08 vs. 0.47±0.08; P<0.001). In subjects with NGT, IGT and patients with diabetes the pulsed Doppler transmitral variables were: E wave (0.72±0.16cm/s vs. 0.62±0.13cm/s vs. 0.58±0.17cm/s; P<0.001), A-wave (0.61±0.13cm/s vs. 0.62±0.11cm/s vs. 0.71±0.14cm/s; P=0.006) and E/A ratio (1.22±0.33 vs. 1.02±0.24 vs. 0.85±0.26; p<0.001). The proportion of subjects with an E/A ratio <1 was 27.6% in the group with NGT, 55% in the group with IGT and 75.7% in the group with diabetes (P<0.001). The E/A ratio correlated with HOMA-IR (r=-0.30, p=0.001) and QUICKI (r=0.37, p<0.001). Multiple linear regression model showed that IR (assessed by QUICKI) was an independent correlate of diastolic dysfunction (P=0.034).

Conclusions: In subjects with impaired glucose tolerance and patients with type 2 diabetes, insulin resistance is associated with impaired diastolic function of the left ventricle.

8. ÖSSZEFOGLALÓ

Cél: A tanulmány célja, hogy kapcsolatot keressen az inzulin rezisztencia (IR) és a bal kamra diasztolés funkciója között 2-es típusú diabétesz betegeknél illetve csökkent glukóz tolerancia esetén.

Módszer: A tanulmány 119 személyre terjedt ki, ők átestek a terheléses vércukor vizsgálaton (OGTT). Az inzulin rezisztenciát a homeosztázis modell becslési módszerrel (HOMA-IR) és a mennyiségi inzulin érzékenységi ellenőrző módszerrel (QUICKI) mértük. A bal kamrai diasztolés funkciót a transthoracalis Doppler echocardiográfiával mértük.

Eredmények: A vércukor vizsgálat (OGTT) 29 esetben normál glukóz toleranciát (NGT), 20 esetben csökkent glukóz toleranciát (IGT), míg 70 esetben 2-es típusú diabéteszt mutatott ki. Lényeges különbségek mutatkoztak az NGT, az IGT és a diabétesz csoport pácienseinek eredményei között a HOMA index (4.20±1.20 vs. 6.45±3.83 vs. 8.70±6.26; P<0.001) és a QUICKI index esetében (0.54±0.11 vs. 0.49±0.08 vs. 0.47±0.08; P<0.001). A pulzatilis Doppler transzmitrális változók az NGT, az IGT és a diabétesz csoportban a következők voltak: E hullám (0.72±0.16 cm/s vs. 0.62±0.13 cm/s vs. 0.58±0.17 cm/s; P<0.001), A hullám (0.61±0.13 cm/s vs. 0.62±0.11 cm/s vs. 0.71±0.14 cm/s; P=0.006) és E/A hányados (1.22±0.33 vs. 1.02±0.24 vs 0.85±0.26; p<0.001). Az E/A hányados<1 eredménnyel rendelkezők aránya az NGT csoportban 27.6%, az IGT csoportban 55%, míg a diabétesz csoportban 75.7% volt (P<0.001). Az E/A hányados korrelált a HOMA (r=-0.30, p=0.001) és a QUICKI mutatóval (r=0.37, p=0.001). A többváltozós regressziós modell azt mutatta, hogy az inzulin rezisztencia (QUICKI méréssel) a diasztolés funkciózavarnak (P=0.034) egy független korrelációja.

Következtetések: Csökkent glukóz tolerancia esetén, 2-es típusú diabéteszes pácienseknél az inzulin rezisztencia a bal kamra csökkent diasztolés funkciójával összefüggésben van.

9. REFERENCES

1. Malecki MT, Klupa T. Type 2 diabetes mellitus: from genes to disease. Pharmacol Rep 2005; 57 Suppl: 20-32.
2. Powers AC. Diabetes mellitus. In Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL. Harrison's principles of internal medicine. 16th ed. McGraw-Hill Companies, Inc., 2005; 2152-80.
3. Frier BM, Fisher BM. Diabetes mellitus. In Haslett C, Chilvers ER, Boon NA, Colledge NR. Davidson's principles and practice of medicine. 19th ed. Churchill Livingstone, 2002; 641-82.
4. Report of a WHO Consultation, Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications, Geneva 1999.

5.Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature 2001; 414: 782–87.

6.King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. Diabetes Care 1998; 21: 1414–31.

7.World Health Organization Expert Committee. Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO consultation, part 1: diagnosis and classification of diabetes mellitus. Geneva: World Health Organization, 1999.

8.Kahn CR: Insulin action, diabetogenes, and the cause of type II diabetes. Diabetes, 1994, 43, 1066–1082.

9.Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. Lancet 2005; 365: 1333–46

10. Pierce M, Keen H, Bradley C. Risk of diabetes in offspring of parents with non-insulin-dependent diabetes. Diabet Med 1995; 12: 6–13.
11. Tattersal RB, Fajans SS. Prevalence of diabetes and glucose intolerance in 199 offspring of thirty-seven conjugal diabetic parents. Diabetes 1975; 24: 452–62.
12. Bliss M. The history of insulin Diabetes Care. 1993; 16: Suppl 3:4-7.

13. Malaisse WJ. Insulin biosynthesis and secretion in vitro. In: Alberti KGMM, Zimmet P, Defronzo RA & Keen H (Hon) editors. International Textbook of Diabetes Mellitus (2nd ed) John Wiley & Sons, New York; 1997 p. 315-36.
14. Home PD. Insulin therapy. In: Alberti KGMM, Zimmet P, Defronzo RA editors & Keen H (Hon) editor International Textbook of Diabetes Mellitus (2nd ed) John Wiley & Sons, New York; 1997 p. 899-928.
15. Dodson G, Steiner D. The role of assembly in insulin's biosynthesis. Curr Opin Struct Biol 1998; 8: 189-94.
16. Schroder D, Zuhlke H. Gene technology, characterization of insulin gene and the relationship to diabetes research. Endokrinologie1982; 79: 197-209.
17. De Lonlay, Saudubray J-M. Persistent hyperinsulinaemic hypoglycaemia. In: Fernandes J, Sudubray J-M, van den Berghe editors Inborn Metabolic Diseases: Diagnosis and treatment. (3rd ed): Springer, Heidelberg Germany; 2000 p.117-26.
18. Soria B, Quesada I, Ropero AB, Pertusa JA, Martin F, Nadal A. Novel players in pancreatic islet signaling: from membrane receptors to nuclear channels. Diabetes 2004; 53 Suppl 1: S86-91.
19. Bratanova-Tochkova TK, Cheng H, Daniel S, et al. Triggering and augmentation mechanisms, granule pools, and biphasic insulin secretion. Diabetes 2002; 51 Suppl. 1: S83-90.
20. Kahn SE, McCulloch DK, Porte D. Insulin secretion in the normal and diabetic human. In: Alberti KGMM, Zimmet P, Defronzo RA, editors & Keen H, (hon) editor. International Textbook of Diabetes Mellitus. (2nd ed) John Wiley & Sons, New York; 1997 p. 337-54.
21. Chen M, Porte D Jr. The effect of rate and dose of glucose infusion on the acute insulin response in man. J Clin Endocrinol Metab 1976; 42: 1168-75.
22. Burks DJ, White MF. IRS proteins and beta-cell function. Diabetes. 2001; 50 Suppl 1: S140-5.
23. Karam JH. Pancreatic Hormones and Diabetes Mellitus. In: Greenspan FS, Strewler GJ, editors. Basic and Clinical Endocrinology. Appleton & Lange, Stamford CT USA; 1997 p. 601-2.

24. Bergman RN. Lilly lecture 1989. Toward physiological understanding of glucose tolerance. Minimal-model approach. *Diabetes* 1989; 38: 1512–27.
25. Ploulin PF. The importance of diabetes as a cardiovascular risk factor. Int J Clin Pract 2000; 110 (Suppl): 3-8.
26. Webster MW, Scot RS. What cardiologists need to know about diabetes? Lancet 1997; 350 (suppl I): 23-28.
27. Wilcox G. Insulin and Insulin Resistance Clin Biochem Rev Vol 26 May 2005 I 21
28. World Health Organization. Obesity: Preventing and Managing the Global Epidemic Report of a WHO Consultation Technical Report Series. World Health Organization, Geneva 2000.
29. Cefalu WT. Insulin resistance: cellular and clinical concepts. Exp Biol Med (Maywood). 2001; 226: 13-26.
30. Reaven G. The metabolic syndrome or the insulin resistance syndrome? Different names, different concepts, and different goals. Endocrinol Metab Clin North Am. 2004; 33: 283-303.
31. Given BD, Mako ME, Tager H, et al. Diabetes due to secretion of an abnormal insulin. N Engl J Med 1980; 302: 129-35.
32. Insel PA, Liljenquist JE, Tobin JD, Sherwin RS, Watkins P, Andres R, Berman M. Insulin control of glucose metabolism in man: a new kinetic analysis. J Clin Invest. 1975; 55: 1057-66.
33. Olefsky JM. Insulin binding, biologic activity and metabolism of biosynthetic human insulin. Diabetes Care 1981; 4: 244-7.
34. Olefsky JM. LIlly lecture 1980. Insulin resistance and insulin action. An in vitro and in vivo perspective. Diabetes 1981; 30: 148-62.
35. Reaven GM, Bernstein R, Davis B, Olefsky JM. Nonketotic diabetes mellitus: insulin deficiency or insulin resistance? Am J Med. 1976; 60: 80-8.
36. Bogardus C, Lillioja S, Howard BV, Reaven G, Mott D.Relationships between insulin secretion, insulin action, and fasting plasma glucose concentration in nondiabetic and noninsulin-dependent diabetic subjects. J Clin Invest 1984; 74: 1238-46.

37. Reaven GM: Insulin resistance and its consequences. In Diabetes Mellitus: A Fundamental and Clinical Text. 3rd ed. LeRoith D, Taylor SI, Olefsky JM, Eds. Philadelphia, Lippincott, Williams & Wilkins, 2004, p. 899–915.
38. Bergman RN, Finegood DT, Ader M. Assessment of insulin sensitivity in vivo. Endocr Rev. 1985; 6: 45-86.
39. DeFronzo RA, Ferrannini E. The pathogenesis of non-insulin-dependent diabetes: an update. Medicine 1982; 61: 125-40.
40. Katz DL. Lifestyle and dietary modification for prevention of heart failure. Med Clin North Am 2004; 88: 1295-320.
41. Laakso M, Lehto S. Epidemiology of macrovascular disease in diabetes. Diabetes Rev 1997; 5: 294-315.
42. Colucci WS, Braunwald E: Pathophysiology of heart failure, in *Heart Disease*, 5th ed, E Braunwald (ed). Philadelphia, Saunders, 1997, pp394-415.
43. Little WC, Braunwald E: Assessment of cardiac function, in Heart Disease, 6th ed, E Braunwald (ed). Philadelphia, Saunders, 1997, pp421-41.
44. Hamby RI, Zoneraich S, Sherman L. Diabetic cardiomyopathy. JAMA 1972; 229: 1749–54
45. Regan TJ, Lyons MM, Ahmed SS, Levinson GE, Oldewurtel HA, Ahmad MR, Haider B. Evidence for cardiomyopathy in familial diabetes mellitus. J Clin Invest 1977; 60: 884–99.
46. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A. New type of cardiomyopathy associated with diabetic glomerulosclerosis. Am J Cardiol 1972; 8; 30: 595-602.
47. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: The Framingham Study. Am J Cardiol 1976; 34: 29–34.
48. Kannel WB, McGee DL. Diabetes and glucose intolerance as risk factors for cardiovascular disease: The Framingham Study. Diabetes Care 1979; 2: 120–6.
49. Malmberg K, Ryden L. Myocardial infarction in patients with diabetes mellitus. Eur Heart J 1988; 9: 256–64.

50. Herlitz J, Malmberg K, Karlsson B, Ryden L, Hjalmarson A. Mortality and morbidity during a five year follow up of diabetics with myocardial infarction. Acta Med Scand 1988; 24: 31–38
51. Bertoni AG, Tsai A, Kasper EK, Brancati FL. Diabetes and idiopathic cardiomyopathy. Diabetes Care 2003; 26: 2791–95.
52. Hayat SA, Patel B, Khattar RS, Malik RA. Diabetic cardiomyopathy: mechanisms, diagnosis and treatment. Clin Sci 2004; 107: 539-57.
53. Fang ZY, Prins JB, Marwick TH. Diabetic cardiomyopathy: evidence, mechanisms, and therapeutic implications. Endocr Rev 2004; 25: 543-67.
54. Attali JR, Sachs RN, Valensi P, et al. Asymptomatic diabetic cardiomyopathy. Diabetes Res Clin Pract 1988; 4: 183-90.
55. Spector KS. Diabetic cardiomyopathy. Clin Cardiol 1998; 21: 885-7.
56. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic function. Circulation 2002; 19: 1387-93.
57. Zile MR, Gaasch WH. Load-dependent left ventricular relaxation in conscious dogs. Am J Physiol 1991; 261: H691-9.
58. Zile MR, Simsic JM. Diastolic heart failure: diagnosis and treatment. Clin Cornerstone 2000; 3: 13-24.
59. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part II: causal mechanisms and treatment. Circulation 2002; 105: 1503-8.
60. Apstein CS, Morgan JP, Cellular mechanisms underlying left ventricular diastolic dysfunction. In: Gaasch WH, LeWinter MM, eds. Left Ventricular Diastolic Dysfunction and Heart Failure. Philadelphia, Pa: Lea & Febiger; 1994: 3-24.
61. Ingwall JS. Transgenesis and cardiac energetics: new insights into cardiac metabolism.J Mol Cell Cardiol 2004; 37: 613-23.
62. Tian R, Nascimben L, Ingwall JS, Lorell BH. Failure to maintain a low ADP concentration impairs diastolic function in hypertrophied rat hearts. Circulation 1997; 96: 1313-9.

63. Kostin S, Hein S, Arnon E, Scholz D, Schaper J. The cytoskeleton and related proteins in the human failing heart. Heart Fail Rev 2000; 5: 271-80.
64. Cooper G 4th. Cardiocyte cytoskeleton in hypertrophied myocardium. Heart Fail Rev 2000; 5: 187-201.
65. Cazorla O, Freiburg A, Helmes M, et al. Differential expression of cardiac titin isoforms and modulation of cellular stiffness. Circ Res 2000; 86: 59-67.
66. Jalil JE, Doering CW, Janicki JS, Pick R, Shroff SG, Weber KT. Fibrillar collagen and myocardial stiffness in the intact hypertrophied rat left ventricle. Circ Res 1989; 64: 1041-50.
67. Kato S, Spinale FG, Tanaka R, Johnson W, Cooper G 4th, Zile MR. Inhibition of collagen cross-linking: effects on fibrillar collagen and ventricular diastolic function. Am J Physiol 1995; 269: H863-8.
68. Brutsaert DL, Fransen P, Andries LJ, De Keulenaer GW, Sys SU. Cardiac endothelium and myocardial function. Cardiovasc Res 1998; 38: 281-90.
69. Fang ZY, Prins JB, Marwick TH. Diabetic cardiomyopathy: evidence, mechanisms, and therapeutic implications. Endocr Rev 2004; 25: 543-67.
70. Marwik TH. Clinical applications of tissue Doppler imaging: a promise fulfilled. Heart 2003; 89: 1377-8.
71. Sohn DW, Chai IH, Lee DJ, et al. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. J Am Coll Cardiol 1997; 30: 474-80.
72. Nagueh SF, Middleton KJ, Kopelen HA, et al. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997; 30: 1527-33.
73. Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler catheterization study. Circulation 2000; 102: 1788-94.

74. Semeniuk LM, Kryski AJ, Severson DL. Echocardiographic assessment of cardiac function in diabetic db/db and transgenic db/db-hGLUT4 mice. Am J Physiol Heart Circ Physiol 2002; 283: H976– H982.
75. Ganguly PK, Thliveris JA, Mehta A. Evidence against the involvement of nonenzymatic glycosylation in diabetic cardiomyopathy. Metabolism 1990; 39:769–73.
76. Cerutti F, Vigo A, Sacchetti C, Bessone A, Barattia G, Morello M, Casalucci D, Gastaldi L. Evaluation of left ventricular diastolic function in insulin dependent diabetic children by M-mode and Doppler echocardiography. Panminerva Med 1994; 36:109–114.
77. Lind L, Berne C, Andren B, Lithell H. Relationship between diastolic hypertension and myocardial morphology and function in elderly males with diabetes mellitus. Diabetologia 1996; 39:1603–06.
78. Matteucci E, Di Bello V, Giampietro O. Integrated analysis of erythrocyte Na+/H+ antiport activity and left ventricular myocardial function in type I insulin-dependent diabetes mellitus. J Diabetes Complications 1995; 9: 208–11.
79. Shimizu M, Sugihara N, Kita Y, Shimizu K, Shibayama S, Takeda R. Increase in left ventricular chamber stiffness in patients with non-insulin dependent diabetes mellitus. Jpn Circ J 1991; 55: 657-64.
80. Ruddy TD, Shumak SL, Liu PP, Barnie A, Seawright SJ, McLaughlin PR, Zinman B. The relationship of cardiac diastolic dysfunction to concurrent hormonal and metabolic status in type I diabetes mellitus. J Clin Endocrinol Metab 1988; 66: 113-8.
81. Bouchard A, Sanz N, Botvinick EH, Phillips N, Heilbron D, Byrd III BF, Karam JH, Schiller NB. Noninvasive assessment of cardiomyopathy in normotensive diabetic patients between 20 and 50 years old. Am J Med 1989; 87: 160-6.
82. Raev DC. Which left ventricular function is impaired earlier in the evolution of diabetic cardiomyopathy? An echocardiographic study of young type I diabetic patients. Diabetes Care 1994; 17: 633-9.

83. Raev DC. Left ventricular function and specific diabetic complications in other target organs in young insulin-dependent diabetics: an echocardiographic study. Heart Vessels 1994; 9: 121-8.
84. Park JW, Ziegler AG, Janka HU, Doering W, Mehnert H. Left ventricular relaxation and filling pattern in diabetic heart muscle disease: an echocardiographic study. Klin Wochenschr 1988; 66: 773-8.
85. Zarich SW, Arbuckle BE, Cohen LR, Roberts M, Nesto RW. Diastolic abnormalities in young asymptomatic diabetic patients assessed by pulsed Doppler echocardiography. J Am Coll Cardiol 1988; 12: 114-20.
86. Bajraktari G, Rexhepaj N, Bakalli A, Elezi S. Reduced left ventricular diastolic function in asymptomatic patients with non-insulin-dependent diabetes mellitus. Med Arh 2004; 58: 339-341.
87. Bajraktari G, Qirko S, Rexhepaj N, Bakalli A, Beqiri A, Elezi S, Ndrepepa G. Non-Insulin Dependent Diabetes as an Independent Predictor of Asymptomatic Left Ventricular Diastolic Dysfunction. Croat Med J 2005; 46: 225-31.
88. Trost SU, Belke DD, Bluhm WF, Meyer M, Swanson E, Dillmann WH. Overexpression of the sarcoplasmic reticulum Ca(2+)- ATPase improves myocardial contractility in diabetic cardiomyopathy. Diabetes 2002; 51: 1166-71.
89. Brown RA, Filipovich P, Walsh MF, Sowers JR. Influence of sex, diabetes and ethanol on intrinsic contractile performance of isolated rat myocardium. Basic Res Cardiol 1996; 91: 353-60.
90. Joffe II, Travers KE, Perreault-Micale CL, Hampton T, Katz SE, Morgan JP, Douglas PS. Abnormal cardiac function in the streptozotocin-induced non-insulin-dependent diabetic rat: noninvasive assessment with Doppler echocardiography and contribution of the nitric oxide pathway. J Am Coll Cardiol 1999; 34: 2111-19.
91. Poirier P, Bogaty P, Garneau C, Marois L, Dumesnil JG. Diastolic dysfunction in normotensive men with well-controlled type 2 diabetes: importance of maneuvers in echocardiographic screening for preclinical diabetic cardiomyopathy. Diabetes Care 2001; 24: 5-10.

92. Paillole C, Dahan M, Paycha F, Solal AC, Passa P, Gourgon R. Prevalence and significance of left ventricular filling abnormalities determined by Doppler echocardiography in young type I (insulindependent) diabetic patients. Am J Cardiol 1989; 64: 1010-6.
93. Strauer BE, Motz W, Vogt M, Schwartzkopff B. Impaired coronary flow reserve in NIDDM: a possible role for diabetic cardiopathy in humans. Diabetes 1997; 46(Suppl 2): S119-S124.
94. Schannwell CM, Schneppenheim M, Perings S, Plehn G, Strauer BE. Left ventricular diastolic dysfunction as an early manifestation of diabetic cardiomyopathy. Cardiology 2002; 98: 33-9.
95. Fang Z, Najos-Valencia O, Leano R, Marwick T. Patients with early diabetic heart disease demonstrate a normal myocardial response to dobutamine. J Am Coll Cardiol 2003; 42: 446-53.
96. Robillon JF, Sadoul JL, Jullien D, Morand P, Freychet P. Abnormalities suggestive of cardiomyopathy in patients with type 2 diabetes of relatively short duration. Diabete Metab 1994; 20: 473-80.
97. Astorri E, Fiorina P, Contini GA, Albertini D, Magnati G, Astorri A, Lanfredini M. Isolated and preclinical impairment of left ventricular filling in insulin-dependent and non-insulin-dependent diabetic patients. Clin Cardiol 1997; 20: 536-40.
98. Salazar J, Rivas A, Rodriguez M, Felipe J, Garcia MD, Bone J. Left ventricular function determined by Doppler echocardiography in adolescents with type I (insulin-dependent) diabetes mellitus. Acta Cardiol 1994; 49: 435-9.
99. Posner J, Ilya R, Wanderman K, Weitzman S. Systolic time intervals in diabetes. Diabetologia 1983; 24: 249-52.
100. DeFronzo RA. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidaemia and atherosclerosis. Neth J Med 1997; 50:191-7.
101. Eiro M, Katoh T, Sakuma Y, Sakurai K, Suzuki H, Asahi K, Watanabe K, Watanabe T. Insulin resistance highly associates with hypertension in IgA nephropathy. Clin Nephrol 2003; 59:71-8.

102. Hong T, Zhao G, Gao W, Huo Y, Zhu G. Insulin sensitivity and the diffuseness of coronary artery disease in humans. Chin Med J 2002; 115: 1886-8.

103. Snehalatha C, Ramachandran A, Saltyamurthy I, Satyavani K, Sivasankari S, Misra J, Viswanathan V. Association of proinsulin and insulin resistance with coronary artery disease in nondiabetic south Indian men. Diabet Med 2001; 18: 706-8.

104. Nakano S, Kitazawa M, Ito T, Hatakeyama H, Nishizawa M, Nakagawa A, Kigoshi T, Uchida K. Insulin resistant type 2 diabetes is related to advanced autonomic neuropathy. Clin Exp Hypertens 2003; 25: 155-67.

105. Bonora E, Targher G, Alberiche M, et al. Predictors of insulin sensitivity in type 2 diabetes mellitus. Diabet Med 2002; 19: 535-42.

106. Lim SC, Tan BY, Chew SK, Tan CE. The relationship between insulin resistance and cardiovascular risk factors in overweight/ obese non-diabetic Asian adults: the 1992 Singapore National Health Survey. International Journal of Obesity 2002; 26: 1511-6.

107. Mykkanen L, Haffner SM, Ronnemaa T, Bergman RN, Laakso M. Low insulin sensitivity is associated with clustering of cardiovascular disease risk factors. Am J Epidemiol 1997; 146: 315-21.

108. Haffner SM, D'Agostino R Jr, Mykkanen L, Tracy R, Howard B, Rewers M, Selby J, Savage PJ, Saad MF. Insulin sensitivity in subjects with type 2 Diabetes. Relationship to cardiovascular risk factors: the Insulin Resistance Atherosclerosis Study. Diabetes Care 1999; 22: 562-8.

109. Kumaran K, Fall CH, Martyn CN, Vijayakumar M, Stein CE, Shier R. Left ventricular mass and arterial compliance: relation to coronary heart disease and its risk factors in South Indian adults. Int J Cardiol 2002; 83: 1-9.

110. Sasso FC, Carbonara O, Cozzolino D, Rambaldi P, Mansi L, Torella D, Gentile S, Turco S, Torella R. Salvatore T. Effects of insulin-glucose infusion on left ventricular function at rest and during dynamic exercise in healthy subjects and noninsulin dependent diabetic patients: a radionuclide ventriculographic study. J Am Coll Cardiol 2000; 36: 219-26.

111. Galderisi M, Paolisso G, Tagliamonte MR, Alfieri A, Petrocelli A, de Divitiis M, Varricchio M, de Divitiis O. Is insulin action a determinant of left ventricular relaxation in uncomplicated essential hypertension? J Hypertens 1997; 15: 745-50.

112. Guida L, Celentano A, Iannuzzi R, Ferrara LA. Insulin resistance, ventricular mass and function in normoglycaemic hypertensives. Nutr Metab Cardiovasc Dis 2001; 11:306-11.

113. Nagano N, Nagano M, Yo Y, Iiyama K, Higaki J, Mikami H, Ogihara T. Role of glucose intolerance in cardiac diastolic function in essential hypertension. Hypertension 1994; 23: 1002-5.

114. Salonen JT, Salonen R. Ultrasound B-mode imaging in observa-tional studies of atherscleroticprogression. Circulation 1993; 87 (Suppl II): 56-65.

115. Suzuki M, Shinozaki K, Kanazawa A, Hara Y, Hattori Y, Tsushima M, Harano Y. Insulin resistance as an independent risk factor for carotid wall thinkening. Hypertension 1996; 28: 593-8.

116. Pergola GD, Ciccone M, Pannacciulli N, Modugno M, SciaraffiaM, Minenna A, Rizzon P, Giorgino R. Lower insulin sensitivity as an independent risk factor for carotid wall thickening in normoten-sive, non-diabetic, non-smoking normal weight and obese premenopausal women. Int J Obes Relat Metab Disord 2000; 24: 825-9.

117. WHO: Definition, diagnosis and classification of diabetes mellitus and its complications. World Health Organization, Department of Noncommunicable Disease Surveillance, Geneva, 1999.

118. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-9.

119. Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, Quon MJ. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 2000; 85: 2402-2410.

120. Yudkin JS. The United Kingdom Prospective Diabetes Study - everything you needed to know about diabetes but were afraid to ask?. Eur Heart J 1999; 20:781-783.

121. Yudkin JS. Vascular events and diabetes: acute myocardial infarction and stroke. In Alberti KGMM, Zimmet P, de Fronzo R, Keen H, eds. International textbook of diabetes. Chichester: Wiley 1997, pp1255-1279.

122. Galderisi M, Anderson KM, Wilson PW, Levy D. Echocardiographic evidence of the existence of a distinct diabetic cardiomyopathy (the Framingham Heart Study). Am J Cardiol 1991; 68: 85-9.

123. Vered A, Battler A, Segal P, Liberman D, Yerushalmi Y, Berezin M, Neufeld HN. Exercise-induced left ventricular dysfunction in young men with asymptomatic diabetes mellitus (diabetic cardiomyopathy). Am J Cardiol 1984; 54: 633-7.

124. Carlstrom S, Karelfors T. Haemodynamic studies on newly diagnosed diabetics before and after insulin treatment. Br Heart J 1970; 32:355–8.

125. Ahmed SS, Jaferi GA, Narang RM, Regan TJ. Preclinical abnormality of left ventricular function in diabetes mellitus. Am Heart J 1975; 89: 153–8.

126. Zoneraich S, Zoneraich O, Rhee JJ. Left ventricular performance in diabetic patients without clinical heart disease. Evaluation by systolic time intervals and echocardiography. Chest 1977; 72: 748–51.

127. Shapiro LM, Howat AP, Calter MM. Left ventricular function in diabetes mellitus. I Methology and prevalence and spectrum of abnormalities. Br Heart J 1981; 45:122–8.

128. Alraksmen J, Ikaheimo M, Kaila J, Linnaluoto M, Takkunen J. Impaired left ventricular filling in young female diabetics. Acta Med Scand 1984; 216: 509–16.

129. Zarich SW, Arbuckle BE, Cohen LR, Roberts M, Nesto RW. Diastolic abnormalities in young asymptomatic diabetic patients assessed by pulsed Doppler echocardiography. J Am Coll Cardiol 1988; 12: 114–20.

130. Paillole C, Cahan M, Paycha F, et al. Procedure and significance of left ventricular filling abnormalities determined by Doppler echocardiography in young type I (insulin-dependent) diabetic patients. Am J Cardiol 1989; 64: 1010–6.

131. Pierce GN, Russell JC. Regulation of intracellular Ca^{2+} in the heart during diabetes. Cardiovasc Res 1997; 34: 41-7.

132. Kawaguchi M, Techigawara M, Ishihata T, Asakura T, Saito F, Maehara K, Maruyama Y. A comparison of ultrastructural changes on endomycardial biopsy specimens obtained from patients with diabetes mellitus with and without hypertension. Heart Vessels 1997; 12: 267-74.

133. Rubler S, Sajadi MR, Araoye MA, Holford FD. Noninvasive estimation of myocardial performance in patients with diabetes. Effect of alcohol administration. Diabetes 1978; 27: 127–134.

134. Hamby RI, Zoneraich S, Sherman L. Diabetic cardiomyopathy. JAMA 1974; 229: 1749–54.

135. Factor SM, Okun EM, Minase T. Capillary microaneurysms in the human diabetic heart. N Engl J Med 1980; 302: 384–8.

136. Stone PH, Muller JE, Hartwell T, York BJ, Rutherford JD, Parker CB, Turi ZG, Strauss HW, Willerson JT, Robertson T, et al. The effect of diabetes mellitus on prognosis and serial left ventricular function after acute myocardial infarction: contribution of coronary disease and diastolic left ventricular dysfunction to the adverse prognosis. J Am Coll Cardiol 1989; 14: 49-57.

137. Grossman W. Diastolic dysfunction in congestive heart failure. N Engl J Med 1991;325:1557-1564.

138. Brutsaert DL, Sys SU. Diastolic dysfunction in heart failure. J Cardiac Failure 1997; 3: 225-42.

139. Mustonen JN, Uusitupa MI, Laakso M, Vanninen E, Lansimies E, Kuikka JT, Pyorala K. Left ventricular systolic function in middle-aged patients with diabetes mellitus. Am J Cardiol 1994; 73: 1202-8.

140. Vanninen E Mustonen J, Vainio P, Lansimies E, Uusitupa M. Left ventricular function and dimensions in newly diagnosed non-insulin-dependent diabetes mellitus. Am J Cardiol 1992; 70: 371-8.

141. Shehadeh A, Regan TJ.Cardiac consequences of diabetes mellitus. Clin Cardiol 1995; 18: 301-5.

142. Devereux RB, Roman MJ, Paranicas M, O'Grady MJ, Lee ET, Welty TK, Fabsitz RR, Robbins D, Rhoades ER, Howard BV. Impact of diabetes on cardiac structure and function: the strong heart study. Circulation 2000; 101: 2271-6.

143. Bauters C, Lamblin N, Mc Fadden EP, Van Belle E, Millaire A, de Groote P. Influence of diabetes mellitus on heart failure risk and outcome. Cardiovasc Diabetol 2003; 2: 1-16.

144. Candido R, Forbes JM, Thomas MC, Thallas V, Dean RG, Burns WC, Tikellis C, Ritchie RH, Twigg SM, Cooper ME, Burrell LM. A breaker of advanced glycation end products attenuates diabetes-induced myocardial structural changes. Circ Res 2003; 92: 785-92.

145. Lagadic-Gossmann DL, Buckler KJ, Le Prigent K, Feuvray D: Altered Ca2+ handling in ventricular myocytes isolated from diabetic rats. Am J Physiol 1996;270: H1529–H1537.

146. Ren J, Davidoff AJ: Diabetes rapidly induces contractile dysfunctions in isolated ventricular myocytes. Am J Physiol 1997;272: H148–H158.

147. Ingelsson E, Sundstrom J, Arnlov J, Zethelius B, Lind L. Insulin resistance and risk of congestive heart failure. JAMA 2005; 294: 334-41.

148. Basta G, Schmidt AM, De Caterina R. Advanced glycation end products and vascular inflammation: implications for accelerated atherosclerosis in diabetes. Cardiovasc Res 2004; 63: 582-92.

149. Jyothirmayi GN, Soni BJ, Masurekar M, Lyons M, Regan TJ. Effects of metformin on collagen glycation and diastolic dysfunction in diabetic myocardium. J Cardiovasc Pharmacol Ther 1998; 3: 319-26.

150. Holmang A, Yoshida N, Jennische E, Waldenstrom A, Bjorntorp P. The effects of hyperinsulinaemia on myocardial mass, blood pressure regulation and central haemodynamics in rats. Eur J Clin Invest 1996; 26: 973-8.

151. DeFronzo RA, Cooke CR, Andres R, Faloona GR, Davis PJ. The effect of insulin on renal handling of sodium, potassium, calcium, and phosphate in man. J Clin Invest 1975; 55: 845-55.

152. Anderson EA, Hoffman RP, Balon TW, Sinkey CA, Mark AL. Hyperinsulinemia produces both sympathetic neural activation and vasodilation in normal humans. J Clin Invest 1991; 87: 2246-52.

153. Gaboury CL, Simonson DC, Seely EW, Hollenberg NK, Williams GH. Relation of pressor responsiveness to angiotensin II and insulin resistance in hypertension. J Clin Invest 1994; 94: 2295-300.

154. Mizushige K, Yao L, Noma T, Kiyomoto H, Yu Y, Hosomi N, Ohmori K, Matsuo H. Alteration in left ventricular diastolic filling and accumulation of myocardial collagen at insulin-resistant prediabetic stage of a type II diabetic rat model. Circulation 2000; 101: 899-907.

155. Goldstein RH, Poliks CF, Pilch PF, Smith BD, Fine A. Stimulation of collagen formation by insulin and insulin-like growth factor I in cultures of human lung fibroblasts. Endocrinology 1989; 124: 964-970.

156. Ito H Hiroe M, Hirata Y, Tsujino M, Shichiri M. Insulin-like growth factor-I induces cardiac hypertrophy with enhanced expression of muscle specific genes in cultured rat cardiomyocytes. Circulation 1993; 87: 1715–21.

10. ACKNOWLEDGEMENT

This research study would have been impossible without a generous help and encouragement offered form many people, professors, colleagues and, last but not least, my own family.

At the outset, however, my deep feelings of sorrow for the late Professor Maria Zsofia Koltai force me to express the most sincere condolences for her, her family and the Faculty where I met her for the first time back in 2000. Then, she accepted to be my mentor and supervise my work. I could not imagine that she would not be present at my last moments completing the work. It has been her personal contribution the very title and the frame of my study. I remain eternally indebted to her. I will never forget her voice pronouncing advises and giving the directions of my work. She ever spared a minute of her time to share it with me, to be throughout the framing process of my work. I would certainly owe her the most hearfelt apologies for her precious time she devoted to me and the work I was doing while she was still alive. May she rest in peace with my love and affections, and the appreciation of my family for her gentle, correct and subtle approach to myself as a foreigner.

Many thanks and very kind regards go for Professor Ferenc Horkay, my second supervisor of this study for having patience to revise this thesis with admirable excellence and speed. His constructive comments were highly useful and I do appreciate throughout my work.

My family friend, Professor Gjin Ndrepepa, deserved special thanks for his unreserved help, professional comments and scholarly devotion to my work any time I asked that from him. It is fir sure that without Professor Ndrepepa, a renown scholar from Muncih in Germany, my study would have had divergent destinity and shape. It is equally sure that quality of my work would have been of dubious nature.

In line with this, I have to say many thanks to one more family friend of mine, Prof. Spiro Qirko, a respected professor at the Faculty of Medicine, University of Tirana, who

encouraged me to continue this study and PhD. His advice has been a guideline for my work and an encouragement worth anything.

My colleague and peer, Dr. Shpend Elezi deserves special thanks for his readiness to be with me for any advise and help I needed. I admit I have misused our private friendship overly, but this study would have not been completed without his endorsement of my hard efforts during the work.

I also owe my utmost sincere gratitude to the entire staff of the Second Division of Cardiology, Internal Medicine Clinic, and the Department of Physiology, in from the University Clinical Centre of Kosova in Prishtina for showing an understanding, and for their supporting, towards my research work.

I express my appreciation to Dr. Robin Chung from Brompton Royal Hospital, London, UK, for revising and editing the English version of my work.

The patients and their families who participated in these studies are cordially thanked for having shown such understanding for research work thus making this work possible.

I thank all my friends for sharing their views with me and for their support during these years.

My parents, my brothers and sisters, and relatives are warmly thanked for their unconditional love, wisdom of life and also practical help with my work.

Last but not least, my deepest and warmest gratitude I wish to express to my close family, my wife Kumrije and my dear children Artan and Ermir, who have given me more joy than I ever imagined, making possible and giving a real meaning to my life. I am sure that I would have not been able to complete this work without their help, encouragement, patience, love and devotion for myself and my work. They all showed a high sense of sacrifice for my work. I do feel indebted eternally for them, their time and efforts devoted to my success.

11. LIST OF PUBLICATIONS

Publications in peer review journals, related to the Ph.D. thesis

1. **Bajraktari G**, Koltai MS, Ademaj F, Rexhepaj N, Qirko S, Ndrepepa G, Elezi S. Relationship between Insulin Resistance and Left Ventricular Diastolic Dysfunction in Patients with Impaired Glucose Tolerance and Type-2 Diabetes. Int J Cardiol. 2006; 110(2): 206-11. **(IF2004: 2.095)**
2. **Bajraktari G,** Qirko S, Rexhepaj N, Bakalli A, Beqiri A, Elezi S, Ndrepepa G. Non-Insulin Dependent Diabetes as an Independent Predictor of Asymptomatic Left Ventricular Diastolic Dysfunction. Croat Med J 2005; 46(2): 225-231. **(IF2004: 0.943)**
3. **Bajraktari G,** Rexhepaj N, Bakalli A, Elizi S. Reduced left ventricular diastolic function in asymptomatic patients with non-insulin-dependent diabetes mellitus. Med Arh. 2004; 58(6): 339-41. **(IF2004: 0)**
4. **Bajraktari G,** Qirko S, Fusco R, Milazzo A, Xhaxho B, Pezanno A. Transmitral pulsed-Doppler echocardiography is a more accurate technique compared with two-dimensional echocardiography using dobutamine, in patients with one vessel coronary artery disease. Eur J Heart Fail. 2003; 5(1): 63-72. **(IF2005: 3.546)**

Publications in peer review journals, not related to the Ph.D. thesis

1. Ismajli J, Shabani X, Manaj R, Emini M**, Bajraktari G.** Mitral valve prolapse, atrial flutter, and syncope in a young female patient. Med Sci Monit 2006; 12(11): CS110-113. (IF2004: 0)

2. **Bajraktari G**, Emini M, Berisha V, et al. Giant left atrial myxoma in an elderly patient: Natural history over a 7-year period. J Clin Ultrasound 2006; 34(9): 461-463. **(IF2004: 0)**
3. **Bajraktari G**, Kastrati S, Manaj R, Berisha I, Thaqi S, Beqiri A. Acute myocardial infarction in a patient with severe unrecognized mitral stenosis. Med Sci Monit 2006; 12(3): CS24-6. **(IF2004: 0)**
4. Rexhepaj N, **Bajraktari G**, Berisha I, Beqiri A, Shatri F, Hima F, Elezi S, Ndrepepa G. Left and Right Ventricular Diastolic Function in Patients with Rheumatoid Arthritis without Clinically Evident Cardiovascular Disease. Int J Clin Pract 2006; 60(6): 683-8. **(IF2004: 1.223)**
5. **Bajraktari G,** Rexhepaj N, Bakalli A, Shaqiri G, Osmani E, Vokrri L, Elezi S. Remission of High Output Heart Failure after Surgical Repair of 30 Months Long-standing Arteriovenous Femoral Fistula. Heart Surg Forum. 2005; 8(2): E118-20. **(IF2004: 0.897)**

Publications in non-peer review journals

1. Rexhepaj N, Kamberi L, **Bajraktari G**, Kastrati A, Elezi S. The effect of nitroglycerine in collateral coronary circulation. Praxis Medica 2004; 46(2); 36-41. (language: Albanian).
2. Ndrepepa G, **Bajraktari G**, Rexhepaj N, Elezi S, Kamberi L. The treatment of chronic heart failure. Praxis Medica 2004; 46(1); 3-21. (language: Albanian).
3. **Bajraktari G**, Bakalli A, Ajeti M, Hima F. Ventricular dispersion in anterior wall acute myocardial infarction. Praxis Medica 2001; 43(2): 69-72. (language: Albanian).
4. **Bajraktari G**, Hima F, Dragusha G, Xhaxho B, Qirko S. The effect of tele-diastolic left ventricular pressure on ventricular repolarization dispersion. Praxis Medica 2001; 43: 43-47. (language: Albanian).
5. **Bajraktari G**, Ahmetaj H. Beta-blockers in heart failure. Praxis Medica 2001; 43: 7-10. (language: Albanian).

6. **Bajraktari G**, Hima F, Qirko S, Fusco R, Milazzo A, Pezzano A. Identification of coronary artery disease by dobutamine stress-echocardiography. Praxis Medica 1999; 42: 3-10. (language: Albanian).
7. **Bajraktari G**, Hima F. The assessment of left ventricular diastolic dysfunction by echocardiography. Praxis Medica 1998; 41: 51-54. (language: Albanian).
8. **Bajraktari G**, Goda A. Atrium commune with abnormal vena cava inferior. Praxis Medica 1998; 41: 41-43. (language: Albanian).
9. Xhaxho B, **Bajraktari G**, Ndrepepa G, Kastrati A. Head-up tilt test in detecting syncopes with unknown origin. Praxis Medica 1997; 40: 9-16. (language: Albanian).
10. Xhaxho B, **Bajraktari G**, Ndrepepa G, Kastrati A. The importance of head-up tilt test in diagnosis and treatment of syncopes with unknown origin. Praxis Medica 1997; 40: 5-8. (language: Albanian).

Abstracts related to the Ph.D. thesis, published in peer review journals

1. **Bajraktari G,** Rexhepaj N, Bakalli A, Elezi S. Relationship between insulin resistance and left ventricular diastolic function in asymptomatic type-2 diabetes patients. EUROCHO – 8th Annual Meeting of the European Association of Echocardiography; ***Athens, Greece***; 1-4 December, 2004. Eur J Echocardiogr 2004; 5 (Suppl 1): 1-185. **(IF2004: 0).**
2. Rexhepaj N, **Bajraktari G**, Bakalli A, Elezi S. Correlation between linsulin resistance and left ventricular diastolic function in asymptomatic type-2 diabetes patients- the role of body-mass index. 16th Annual Meeting of Mediterranean Association of Cardiology and Cardiac Surgery. ***Bodrum, Turkey***; 26-30 September, 2004. Heart Surg Forum. 2004; 7(supl). **(IF2004: 0.897)**
3. **Bajraktari G**, Nura A, Rexhepaj N, Bakalli A. Effect of fasting glucosae level on Left Ventricular Diastolic Function in Asymptomatic Patients with Non-Insulin-Dependent Diabetes Mellitus. 3rd Congress of Cardiologists and Angiologists of

Bosnia and Herzegovina with International Participation; ***Tuzla, Bosnia and Herzegovina***; 27-30 May, 2004. Med Arh 2004; 58 (2, supl).1): 1-96. **(IF2004: 0).**

4. **Bajraktari G**, Rexhepaj N, Bakalli A, Elezi S. Insulin Resistance in Asymptomatic Type-2 Diabetes Patients-The Role of Obesity. 5th Congress of the Croatian Cardiac Society; ***Opatija, Croatia***; 16-19 May, 2004. Lijec Vjesn 2004; 126 (supl.1). **(IF2004: 0).**
5. **Bajraktari G**, Nura A, Rexhepaj N, Bakalli A, Elezi S. The effect of insulin resistance on left ventricular diastolic function in asymptomatic type-2 diabetes patients. 8th World Congress of Echocardiography and Vascular Ultrasound; ***Antalya, Turkey***; 6-9 May, 2004. Echocardiography 2004; 21 (suppl). **(IF2004: 0.877).**
6. **Bajraktari G**, Qirko S, Bakalli A, Zeqiri N, Rexhepaj N, Ajeti M, Hima F. Detection of pseudonormalization of left ventricular diastolic dysfunction by color m-mode echocardiography in asymptomatic non-insulin-dependent diabetes mellitus patients. EUROCHO - 7th Annual Meeting of the European Association of Echocardiography; ***Barcelona, Spain***; 3-6 December, 2003. Eur J Echocardiogr 2003; 4 (Suppl 1). **(IF2004: 0).**
7. **Bajraktari G**, Qirko S, Hima F, Bakalli A, Ajeti M, Rexhepaj N, Zeqiri N. Left ventricular diastolic dysfunction and other complications in asymptomatic non-insulin-dependent diabetes mellitus patients. European Society Congress 2003; ***Vienna, Austria;*** 30 August- 3 September, 2003. Eur Heart J 2003; 24 (suppl). **(IF2005:7.431)**
8. **Bajraktari G**, Bakalli A, Ajeti M, Hima F. Pseudonormalization of left ventricular diastolic dysfunction in asymptomatic non-insulin-dependent diabetes mellitus patients. 18th National Congress of Turkish Society of Cardiology. ***Antalya, Turkey***; 5-8 October, 2002. Turk Kardiyol Dern Ars 2002; 30 (supl.). **(IF2004: 0).**
9. Bakalli A, **Bajraktari G** , Ajeti M, Hima F. Diabetic neuropathy and retinopathy in asymptomatic non-insulin-dependent diabetes mellitus patients. 18th National Congress of Turkish Society of Cardiology. ***Antalya, Turkey***; 5-8 October, 2002. Turk Kardiyol Dern Ars 2002; 30 (supl.). **(IF2004: 0).**

10. **Bajraktari G** , Fusco R, Milazzo A, Xhaxho B, Qirko S, Pezzano A. Transmitral pulsed-Doppler echocardiography is more accurate technique compared with 2-dimensional echocardiography using dobutamine, for detecting patients with one-vessel coronary artery disease. Heart failure '99 meeting. ***Goteburg, Sweden***; 5-8 June 1999. Eur J Heart Fail 1999; 1(1): 1-89. **(IF2005: 3.546).**
11. **Bajraktari G** , Fusco R, Milazzo A, Xhaxho B, Qirko S, Pezzano A. Correlation of pulsed-Doppler left ventricular filling variables changes with haemodynamic changes during dobutamine stress echocardiography. Heart failure '99 meeting. ***Goteburg, Sweden***; 5-8 June 1999. Eur J Heart Fail 1999; 1(1): 1-89. **(IF2005: 3.546).**

Abstracts not related to the Ph.D. thesis published in peer review journals

1. **Bajraktari G,** Duncan A, Henein M**.** Predictors of Cardiac Events in Patients Undergoing Coronary Artery By-Pass Surgery. EUROCHO – 10th Annual Meeting of the European Association of Echocardiography; ***Prague, Czech Republic***; 6-9 December, 2006. Eur J Echocardiogr 2006; 7 (Suppl 1). **(IF2004: 0).**
2. **Bajraktari G,** Emini M, Shabani X, et al. The Prognostic Significance of the Presence and Severity of Mitral Regurgitation for Survival in Patients with Chronic Heart Failure. World Congress of Cardiology. ***Barcelona, Spain;*** 2-6 September 2006. Eur Heart J 2006; 27 (suppl). **(IF2005:7.431)**
3. Beqiri A, **Bajraktari G**, Selmani H, et al. Left bundle branch block and myocardial performance index in patients with dilatative cardiomyopathy. 14th Alpe Adria Cardiology Meeting. ***Cavtat-Dubrovnik, Croatia;*** 3-7 May, 2006. Lijec Vjesn 2006; 128 (supl.1). **(IF2004: 0).**
4. Kastrati S, Manaj R, Berisha I, Thaci S, Beqiri A, Elezi S, **Bajraktari G**. Acute myocardial infarction in a patient with severe unknown mitral stenosis. 14th Alpe Adria Cardiology Meeting. ***Cavtat-Dubrovnik, Croatia;*** 3-7 May, 2006. Lijec Vjesn 2006; 128 (supl.1). **(IF2004: 0).**

5. **Bajraktari G**, Beqiri A, Selmani H, et al. Increased urea in blood as a predictor in patients with stabile chronic heart failure. 14th Alpe Adria Cardiology Meeting. ***Cavtat-Dubrovnik, Croatia;*** 3-7 May, 2006. Lijec Vjesn 2006; 128 (supl.1). **(IF2004: 0).**
6. **Bajraktari G,** Rexhepaj N, Berisha I, Beqiri A, Shatri F, Elezi S. Left and right ventricular diastolic function in rheumatoid arthritis patients without clinically evident cardiovascular disease. Heart Failure 2005; ***Lisbon, Portugal***; 11-14 June 2005. Eur J Heart Fail 2005; 7(suppl). **(IF2005: 3.546).**
7. **Bajraktari G** , Rexhepaj N, Bakalli A, Shaqiri G, Osmani E, Vokrri L, Elezi S. Remission of high output heart failure after surgical repair of 30 months long-standing arteriovenous femoral fistula. 16th Annual Meeting of Mediterranean Association of Cardiology and Cardiac Surgery. ***Bodrum, Turkey***; 26-30 September, 2004. Heart Surg Forum. 2004; 7(supl). **(IF2004: 0.897)**

Lectures as invited speaker in International Meetings

1. **Bajraktari G.** The Prognostic Role of Total Isovolumic Time in Patients with Coronary Artery Disease. X World Congress Of Echocardiography And Cardiovascular Imaging. ***Rome, Italy***; October 19-21, 2006.
2. **Bajraktari G.** Echocardiographic evaluation of the mitral regurgitation in daily practice. International teaching course on echocardiography: Valvular heart diseases – State of the art. ***Tirana, Albania;*** 14 October 2006.
3. **Bajraktari G.** Mitral valve Endocarditis: How to distinguish vegetations from other abnormalities. 2nd Annual Congress on Cardiology and Cardiac Surgery. ***Bodrum, Turkey***; 20-24 September, 2006.
4. **Bajraktari G**. The prognostic role of total isovolumic time in patients with coronary artery disease. 14th Alpe Adria Cardiology Meeting. ***Cavtat-Dubrovnik, Croatia;*** 3-7 May, 2006.

5. **Bajraktari G.** The diastolic dysfunction in diabetic patients – the role of Doppler echocardiography. International Meeting on Echocardiography. ***Tirana, Albania;*** 24 September 2005.
6. **Bajraktari G.** The prognostic role of myocardial performance index in patients with acute myocardial infarction. IX World Congress of Echocardiography and Vascular Ultrasound. ***Marrakech, Morocco;*** 4-17 September 2005.
7. **Bajraktari G**, New Methods for the assessment of left ventricular function by echocardiography. 16 th Annual Meeting of Mediterranean Association of Cardiology and Cardiac Surgery. ***Bodrum, Turkey***; 26-30 September, 2004.
8. **Bajraktari G**. Primary and secondary prevention by statins. 43rd Romanian Congress of Cardiology***. Poiana Brasov, Romania;*** 15-18 September 2004.
9. **Bajraktari G.** The role of echocardiography in early detecting of diastolic dysfunction in diabetic patients. 3 rd Congress of Cardiologist and Angiologists of Bosnia and Herzegovina. ***Tuzla, Bosnia and Herzegovina***; 27-30 May, 2004
10. **Bajraktari G.** The role of TEE in mitral stenosis. VIII. World Congress of Echocardiography and Vascular Ultrasound. ***Antalya, Turkey***; 6-9 May, 2004.
11. **Bajraktari G.** The role of echocardiography in early detecting of diastolic dysfunction in diabetic patients. VIII World Congress of Echocardiography and Vascular Ultrasound. ***Antalya, Turkey***; 6-9 May, 2004.
12. **Bajraktari G**. The role of diastolic dysfunction screening in NIDDM patients. 1st International Symposium on Echocardiography. ***Ohrid, Macedonia;*** 14-16 September, 2003.