ORIGINAL ARTICLE

Hypertensive acute heart failure and elevated glucose levels

Psirropoulos D, Lefkos N, Boudonas G, Efthimiadis Ap, Tsapas G

Cardiology Unit of the 2nd Department of Internal Medicine, Aristotelian University of Thessaloniki, Hippokration Hospital of Thessaloniki

The role of hypertension and diabetes mellitus as risk factors in coronary heart disease is known but the role of elevated glucose levels in patients who are apparently non-diabetic but suffering from hypertensive heart failure is controversial.

Methods: Sixty eight hypertensive patients under sufficient anti-hypertensive treatment (M=42, F=26, mean age=70+8 years) with heart failure (II-IV NYHA class, EFΘ40%, LAEI<0.6, EPSS>5mm) and without known history of ischaemic heart disease, hyperlipidaemia or diabetes mellitus were studied. In all patients at baseline blood pressure and heart rate were measured, an echocardiogram, for determination of diastolic and systolic indices was performed, and fasting glucose and lipids levels were measured.

Results: Elevated glucose levels were found in 21 patients who consisted Group A and the remaining 47 patients without diabetes consisted Group B. Glucose levels were significantly higher in Group A (180mg/dl) compared to Group B (106mg/dl); systolic dysfunction was also greater in Group A than in Group B (EF=29.4% and EPSS=10.7mm vs.EF=34.2% and EPSS=6.8mm respectively); diastolic dysfunction was also greater in Group A than in Group B (LAEI=0.32 vs. LAEI =0.41); cholesterol levels were higher in Group A than in Group B (224.4mg/dl vs. 204mg/dl); and triglycerides were also higher in Group A than in Group B (216.8mg/dl vs. 189mg/dl). The anti-hypertensive treatment was sufficient without significant differences in both groups.

Conclusions: The hyperglycemia, in our study, shows a clear significant negative effect on the systolic function of the left ventricle in the hypertensive patients. In hypertensive patients with heart failure the endothelial dysfunction and/or the insufficient treatment of diabetes may contribute to appearance of systolic dysfunction of the left ventricle. The coexistence also of diabetes and hyperlipidaemia could indicate underlying coronary arterial disease which may predispose to failure.
Hippokratia 2001, 5 (2): 69-75

Considerable controversy exists regarding impairment of cardiac function in prediabetic conditions[1-3]. The role of arterial hypertension (AH) and diabetes mellitus (DM) as risk factors in coronary arterial disease (CAD) is known but the role of diabetes mellitus and furthermore the role of elevated glucose levels in apparently non-diabetic but suffering from hypertensive heart failure patients is controversial[4-9].

Aim of our cross-sectional, descriptive study was to detect any effect of glucose metabolism disturbances on left ventricular function in hypertensive patients.

METHODS

Two hundred and fifty nine hypertensive patients (M=168, F=91, mean age = 64±14 years) who admitted to our department with successfully treated acute pulmonary oedema (APO) on the ground of hypertensive crisis without known history of CAD (symptoms, ECG alterations, local wall sub-movement by echocardiography, exercise test, angiography), DM, and hyperilipidaemia during the period 1996 to the end of 1999 estimated for their prehospital NYHA class (II-IV class) based on their medical files, history and symptoms (all patients in APO are in NYHA Class IV, by definition). An acute ischaemic episode responsible for APO was excluded based on ECG alterations, serial enzyme and troponin T determination.

One hundred and seventeen patients filled the above criteria in whom an echocardiographic M-mode evaluation of ejection fraction by cubing the sort axis (EF = Stroke Volume / End-diastolic

Volume) was already existed in their medical files that was done during the previous 12 months. The patients with EF≤40% entered the study.

Patients with heart valve diseases, renal diseases, and atrial fibrillation excluded from the study.

Finally, sixty eight (68) hypertensive patients (M=42, F=26, mean age=70±8 years) under sufficient anti-hypertensive treatment (Table 1), based on their medical files, during the last six months (Blood pressure control seemed to be optimal until that time according to the WHO guidelines) before the last admission entered the study. Although the AH seemed to be sufficiently managed the BP elevation may be attributable to emotional stress or increased workload or non sufficiently filled medical files.

The taken blood samples at the day of patients' discharge (baseline) after at least of four days hospitalization, were estimated for glucose levels, total cholesterol, and triglycerides (Reflotron). Concerning glucose estimation, the IV administration of any dextrose solution was discontinued; as baseline level was considered the mean value of the last two fasting (at least six hours) glucose estimations in different blood samples, performed at the day of discharge.

Our patients were divided into two groups based on baseline glucose levels; Group A consisted from 21 patients (M=8, F=13, mean age=68±9 years) with glucose levels higher than 120 mg/dl whilst the remaining 47 patients (M=34, F=13, mean age=72±10 years) without hyperglycemia composed Group B.

Evaluation of systolic (ejection fraction by cubing the sort axis and mitral E point to ventricular septal separation-EPSS) and diastolic (left atrial emptying index-LAEI) (Figure 1) function of the left ventricle, by means of ultrasound (Aloka SSD 630), was performed in all patients at the day of discharge (Table 2).

The last 36 hours before discharge blood pressure was monitored in all patients every six hours (standing and resting).

Biostatistical analysis was applied using SPSS (Statistical Package for Social Sciences) for Windows, Rel. 10.0 (Student's t test and linear regression analysis).

RESULTS

All parameters were normally distributed.

The mean glucose level was significantly higher in Group A (180.3 ± 34.1 mg/dl) compared to Group B (105.9 ± 7.1 mg/dl). The diastolic function as was estimated by LAEI was impaired especially in Group A compared to Group B (0.32 ± 0.03 vs. 0.41 ± 0.04, $p<0.01$) patients (Table 2); the systolic function was also impaired in Group A (EF=29.4 ± 4.3 %, NS and EPSS=10.8 ± 2.9 mm, $p<0.01$) compared to Group B patients (EF=34.2 ± 2.9 % and EPSS=6.8 ± 1.7 mm) (Table 2). The mean cholesterol and triglycerides levels were higher in Group A (224.4 ± 28.8 mg/dl, NS and 216.8 ± 12.5 mg/dl, $p<0.001$) compared to Group B (204.0 ± 17.4 mg/dl and 189.0 ± 17.3 mg/dl respectively) (Table 2).

The differences in estimated EF before (medical files) and during hospitalization were significant (Table 3).

Linear regression analysis revealed statistically significant correlation between glucose levels and EF values ($r=-0.646$, $p<0.01$, Figure 2), EPSS values ($r=0.602$, $p<0.01$, Figure 3), LAEI values ($r=-0.533$, $p<0.01$, Figure 4), total cholesterol levels ($r=0.447$, $p<0.01$, Figure 5) and triglycerides levels ($r=0.576$, $p<0.01$, Figure 6).

The mean BP measurements where within normal limits without significant differences between two groups ($p<0.5$); the proportion also of drugs used was without differences between groups.

DISCUSSION

Patients with diabetes mellitus are particularly vulnerable to cardiovascular disease[9-11]. Although structural and functional myocardial complications are present in patients with diabetes alone, they are particularly severe in patients with both diabetes and hypertension[8,12-14]. Considerable evidence, both in experimental animal models and in humans, points to hypertension as of critical importance in the pathogenesis of severe diabetic heart disease[16,17]. In diabetic hypertensive cardiomyopathy, CAD as well as structural and functional abnormalities are more pronounced than would expected from either process alone. The myocardial damage is attributed mainly to hypertension, whereas the myocellular dysfunction is attributed mainly to glucose metabolism disturbances[1,17-19]. It is generally accepted that the disturbances of glucose metabolism affect the cardiovascular system through many ways

Table 1. Basic demographic data and hypertensive treatment before hospitalization in both studied groups (hyperglycaemic-Group A and euglycaemic-Group B) of patients.

	Sex	Age	b-blocker	Ca^{++}	ACE	Combinations
Hyperglycaemic n_1=21	M=8 F=13	68±9	5	4	6	6
Euglycaemic n_2=47	M=34 F=13	72±10	12	8	13	14

Table 2. Differences found in parameters studied between hyperglycemic (Group A) and euglycaemic (Group B) patients.

	EF (%)	EPSS (mm)	LAEI	Total-ch (mg/dl)	Trigl/des (mg/dl)
Hyperglycaemic n_1=21	29.4±4.3*	10.8±2.9**	0.32±0.03**	224.4±28.8*	216.8±12.5***
Euglycaemic n_2=47	34.2±2.9	6.8±1.7	0.41±0.04	204.0±17.4	189.0±17.6

* NS, **p<0.01 and *** p<0.001 compared to non-diabetics.

Table 3. Differences found in estimated EF before and during hospitalization.

	EF before (%)	EF (%)
Hyperglycaemic n_1=21	35.3±3.6*	29.4±4.3
Euglycaemic n_2=47	36.8±2.5*	34.2±2.9

*p<0.01 compared to non-diabetics.

(participation in atherosclerotic process, arterial hypertension etc)[3,13,20,21].

Although DM has been long recognized as a major risk factor for CAD, the effect of "elevated" levels to upper normal limits of glucose in people without diabetes has been unclear. Is reported that glucose elevations that remain in the "normal" range may be responsible for more heart attacks than the amount caused by diabetes itself [4,22]. The level and the way that glucose disturbances act on left ventricular function, systolic and diastolic, consist subject for controversies.

Although the blood pressure control seemed to be optimal according to the WHO guidelines this disturbance (oedema) happened suddenly without any obvious predisposing factor and may be due to non close follow-up or to emotional stress and to acute elevation of workload.

The evaluation of our results indicates a statistically greater impairment on systolic and diastolic LV function in hypertensive patients with raised glucose levels than in euglycaemic hypertensive patients (Table 2, Figures 2-4). Our findings are close to other reported data[16,23-25].

The strong relation of glucose levels with the triglycerides and the mild elevation of total cholesterol levels in patients with raised glucose levels suggests that the coexistence of glucose metabolism disturbances and dyslipidaemia may contribute to LV dysfunction probably via predisposition to coronary arterial disease (Figures 5 and 6)[26,27].

In addition, the strong correlation of glucose levels with the indices of LV function confirms the effect of glucose metabolism on these parameters although the EF values appeared statistically non significant between the two groups[28-30]. In contrary to EF, the other LV function indices appeared to be statistically significant affected by raised glucose levels, fact that confirms the sensitivity of these indices in revealing systolic (EPSS) and diastolic (LAEI) dysfunction of the LV[30-40].

Although there is statistically strong evidence of direct influence of elevated glucose levels on LV function in hypertensive patients, the small number of our cases may indicate the need of further investigation; the metabolic pathways that enable this action, need to be declared.

This distinct study, which relates to the prevalence of newly diagnosed DM in a patient population presenting with pulmonary oedema

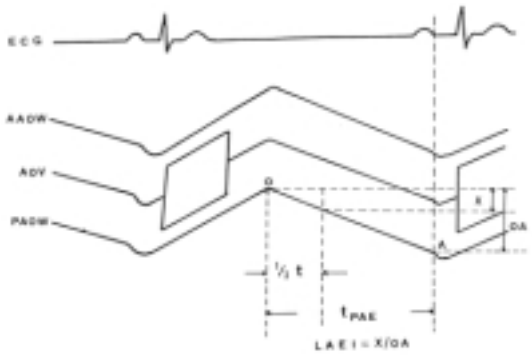

Figure 1. Method of estimation of the left atrial (LA) emptying intex (LAEI). The time of passive atrial emptying (t_{pae}) is defined by the distance between points O and A. Point O corresponds to the onset of LA active emptying, immediately after the electocardiographic P wave.

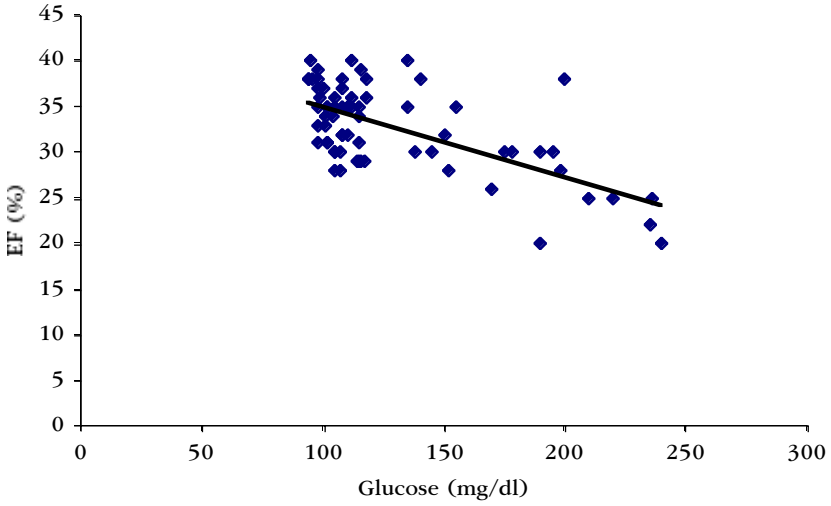

Figure 2. Correlation of glucose to EF (r=-0.646, v=66, p<0.01).

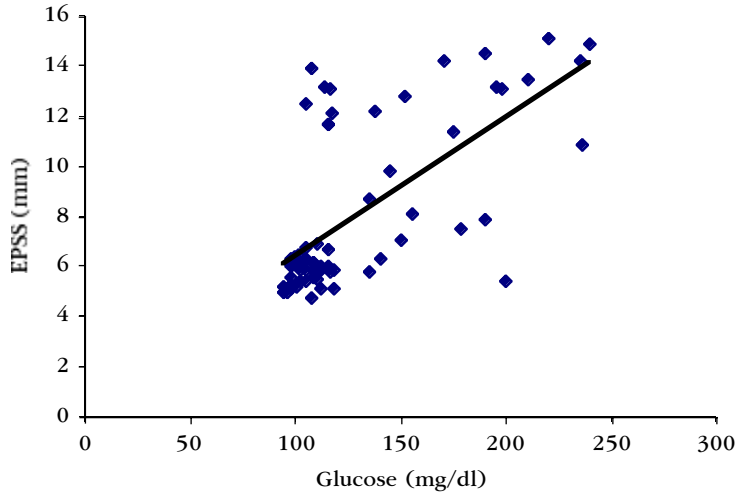

Figure 3. Correlation of glucose to EPSS (r=0.602, v=66, p<0.01).

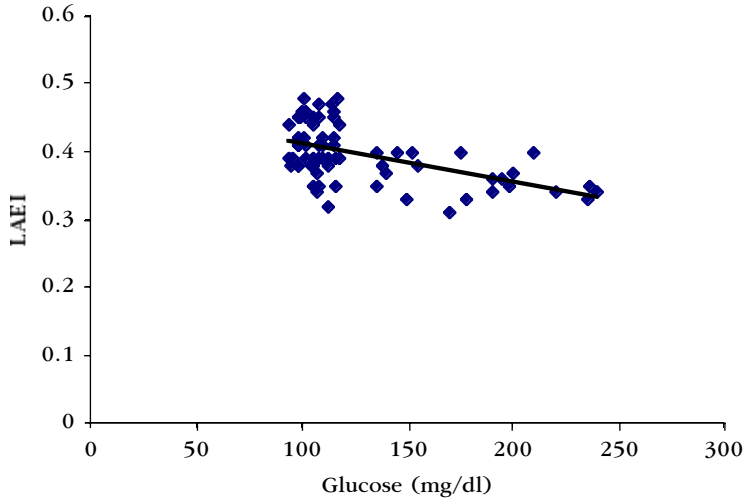

Figure 4. Correlation of glucose to LAEI (r=-0.533, v=66, p<0.01).

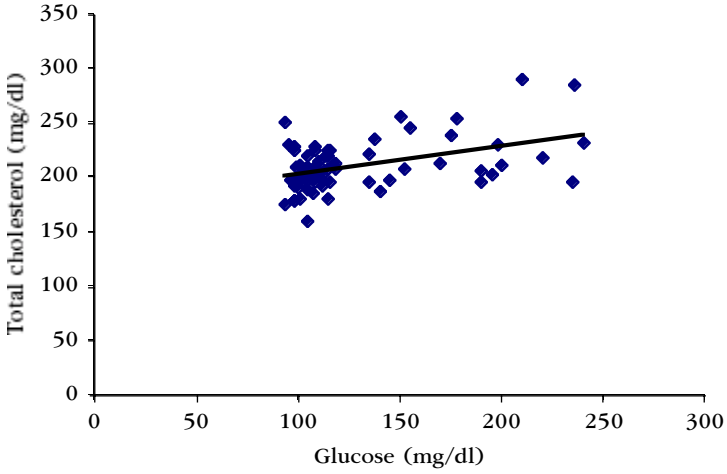

Figure 5. Correlation of glucose to total cholesterol (r=0.447, v=66, p<0.01).

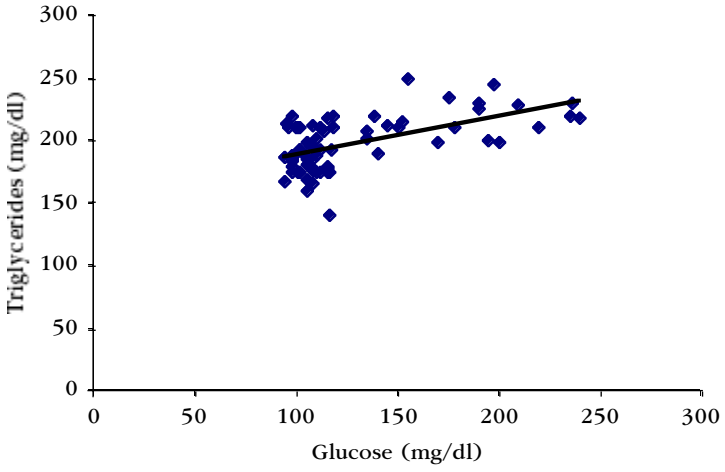

Figure 6. Correlation of glucose to triglycerides (r=0.576, v=66, p<0.01).

and AH, confirms that – in these clinical settings – diabetes mellitus patients have a more pronounced dysfunction of the heart and a poorer prognosis although it was done with crude but easy and cheap M-mode echocardiographic measurements of ejection fraction, of ejection and of filling function, combined with total cholesterol and triglycerides levels.

Our sense is that this study adds no original information on this subject although superficially seems to confirm previous published data.

CONCLUSIONS

The diabetes mellitus, in our study, shows a clear significant negative effect on the left ventricular systolic and diastolic function in the hypertensive patients. In hypertensive patients with heart failure the endothelial dysfunction and/or the insufficient treatment of diabetes mellitus may contribute to the appearance of left ventricular systolic and diastolic dysfunction. Also, the coexistence of diabetes and hyperlipidaemia could predispose to underlying subclinical coronary arterial disease which may contribute to left ventricular failure.

Our results in combination with other reported data would focus attention on the high prevalence of LV function disturbances in hypertensive patients with glucose metabolism disturbances and may lead to innonative ways of preventing adverse episodes in this group of population.

ΠΕΡΙΛΗΨΗ

Δ. Ψυρρόπουλος, Ν. Λευκός, Γ. Μπουντώνας, Απ. Ευθυμιάδης, Γ. Τσάπας. **Υπερτασική καρδιακή ανεπάρκεια και αυξημένα επίπεδα γλυκόζης.** Ιπποκράτεια 2001, 5 (2): 69-75

Ο ρόλος των αυξημένων επιπέδων γλυκόζης σε φαινομενικά μη διαβητικούς ασθενείς που πάσχουν από υπερτασική καρδιακή ανεπάρκεια είναι εν πολλοίς άγνωστος αν και είναι γνωστή η συμμετοχή του σακχαρώδη διαβήτη και της αρτηριακής υπέρτασης ως παραγόντων κινδύνου για την εμφάνιση και εξέλιξη της στεφανιαίας νόσου.

Μελετήθηκαν 68 υπερτασικοί ασθενείς (Α=42, Γ=26, μέση ηλικία=70+8 έτη) υπό φαινομενικά επαρκή αγωγή με καρδιακή ανεπάρκεια (II-IV NYHA class, EF≤40%, LAEI<0.6, EPSS>5mm) και χωρίς γνωστό ιστορικό στεφανιαίας νόσου, δυσλιπιδαιμίας και διαβήτη οι οποίοι νοσηλεύθηκαν για οξεία υπερτασική καρδιακή ανεπάρκεια.

Αυξημένα επίπεδα γλυκόζης βρέθηκαν σε 21 ασθενείς που αποτέλεσαν την ομάδα Α ενώ οι υπόλοιποι 47 αποτέλεσαν την ομάδα Β. Αυξημένα επίπεδα γλυκόζης βρέθηκαν σημαντικά υψηλότερα στην ομάδα Α (180mg/dl) συγκριτικά με την ομάδα Β (106mg/dl). Η συστολική δυσλειτουργία της αριστερής κοιλίας ήταν εντονότερη στην ομάδα Α συγκριτικά με την ομάδα Β (EF=29.4% and EPSS=10.7mm έναντι EF=34.2% and EPSS=6.8mm). Η διαστολική δυσλειτουργία της αριστερής κοιλίας ήταν επίσης εντονότερη στην ομάδα Α συγκριτικά με την ομάδα Β (LAEI=0.32 έναντι LAEI =0.41). Τα επίπεδα της χοληστερόλης ήταν υψηλότερα στην ομάδα Α συγκριτικά με την ομάδα Β (224.4mg/dl έναντι 204mg/dl) όπως επίσης και των τριγλυκεριδίων (216.8mg/dl έναντι 189mg/dl). Δεν υπήρχαν σημαντικές διαφορές στο είδος της αντι-υπερτασικής αγωγής ανάμεσα στις δύο ομάδες.

Τα αυξημένα επίπεδα γλυκόζης φαίνεται ότι σχετίζονται με σημαντική αρνητική επίδραση στην συστολική λειτουργία της αριστερής κοιλίας στους υπερτασικούς ασθενείς.

REFERENCES

1. Groop L, Forsblom G, Lehtovirta M. Characterization of the prediabetic state. Am J Hyperten 1997, 10:9 (Pt2):S172-S180.
2. Marre M, Bouhanick B, Berrnt G. Prediabetic state. Realities and illusions. Presse Med 1969, 77:29:1047-9.
3. Katsufumi M, Li Y, Takahisa N, et al. M: Alteration in left ventricular diastolic filling and accumulation of myocardial collagen in insulin-resistant prediabetic stage of a type II diabetic rat model. Circulation 2000, 101:899-907.
4. Stone PH, Muller JE, Hartweell T. The effect of diabetes mellitus on prognosis and serial left ventricular function after acute myocardial infarction. J Am Coll Cardiol 1989, 14:99-105.
5. Grimaldi A, Gonzalez I, Bosquet F, komajda M. Heart involvement in diabetic patients. Presse Med 1990, 19:11:519-24.
6. Curb JB, Pressel S, Culter JA, et al. Effect of diuretic based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. JAMA 1996, 276:23:1886-92.
7. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. 1997, 36:523-34.
8. Grossman E, Rosenthal T. Hypertensive heart disease and the diabetic patient. Current opinion in Cardiology 1995, 10:458-65.
9. UK Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes. B M J 1998, 7160:703-13.

10. Bhoupatkar H, Simmoms D: Diabetes and hyperglycaemia among patients with congestive cardiac failure in a multiethnic population. N Z Med J 1996, 109:1026:268-70.
11. Haffner SM. Cardiovascular risk factors and the prediabetic syndrome. Ann Med 1996, 28:4:363-70.
12. Shaw JE, Hodge AM, de Courten M, Chiston P, Zimmet PZ. Isolated post-challenge hyperglycaemia confirmed as a risk factor for mortality. Diabetologia 1999, 42:9:1050-4.
13. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Arc Int Med 1997, 157:2413-46.
14. American Diabetes Association. Standards of medical care for patients with diabetes mellitus (Position Statement). Diabetes Care 1998, 21:S50-S53.
15. Ferri C. Treatment of hypertension in diabetes mellitus with or without nefropapthy. Current opinion in Endocrinology and Diabetes 1997, 4:245-51.
16. Cody RJ. Hypertensive heart disease and heart failure. Current opinion in Cardiology 1995, 10:450-7.
17. Yagi K, Kim S, Wanibushi H, Yamashita T, Yakamura Y, Iwao H. Characteristics of diabetes, blood pressure, and cardiac and renal complications in Otsuka Long Evans Tokushima Fatty rats. Hypertension 1997, 29:728-35.
18. Pyoraia K, Pedersen TR, kjekhus J, Faergeman O, Olsson AG, Thorgeirsson G, and the Scandinavian Simvastatin survival Study (4S) Group. cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. Diabetes Care 1997, 20:614-20.
19. Katz DS. Mechanisms and implications of endothelial dysfunction in congestive heart failure. Current opinion in Cardiology 1997, 12:259-64.
20. Jaap AJ, Shore AC, Tooke JE. Relationship of insulin resistance to microvascular dysfunction in patients with fasting hyperglycaemia. Diabetologia 1997, 40:2:238-43.
21. Olivarius NDF, Andreason AH, Keiding N, Mogensen CE. Epidemiology of renal involvement in newly diagnosed middle-aged and elderly diabetic patients. Cross-sectional data from the population-based study "Diabetes care in general practice". Diabetologia 1993, 36:1007-16.
22. Haheim LJ, Holme I, Hjernmann I, Leven P. Nonfasting serum glucose and the risk of fatal stroke in diabetic and nondiabetic subjects. Oslo Study. Stroke 1995, 26:5:774-7.
23. Kawano K, Hirashima T, Mori S, Saitoh Y, Kurosumi M, Natori T. Spontaneous long-term hyperglycemic rat with diabetic complications. Otsuka Long-Evans Tokushima Fatty (OLETF) strain. Diabetes 1992, 41:1422-28.
24. Beck-Nielsen H, Groop LC. Metabolic and genetic characterization of prediabetic states. J Clin Invest 1994, 94:1714-21.
25. Ohno M, Cheng CP, Little WC. Mechanism of altered patterns of left ventricular filling during the development of congestive heart failure. Circulation 1994, 89:2241-50.
26. Simmons D, Williams DD. Random blood glucose as a screening for diabetes in a biethnic population. Diabet Med 1994, 11:9:830-5.
27. Kyner JL, Levy RI, Soeldner JS, Gleason RE, Fredrickson DS. Lipid, glucose and insulin interrelationsships in normal, prediabetic, and chemical diabetic subjects. J Lab Clin Med 1976, 88:3:345-58.
28. Riggs TW, Transue D. Doppler echocardiographic evaluation of left ventricular diastolic function in adolescents with diabetes mellitus. Am J Cardiol 1990, 65:899-902.
29. Celentano A, Vaccaro O, Tammaro P, et al. Early abnormalities of cardiac function in non-insulin-dependent diabetes mellitus. Am J Cardiol 1995, 76:1173-6.
30. Aurigemma GP, Silver KH, Priest MA, Gaasch WH. Geometric changes allow normal ejection fraction despite depressed myocardial shortening in hypertensive left ventricular hypertrophy. J Am Coll Cardiol 1995, 26:195-202.
31. Boudonas G, Lefkos N, Efthimiadis A, Liatsis I, Moulovasili A. Insulin and heart disease. Il Cuore 1995, XII:305-10.
32. Dougherty AH, Naccarelli GV, Gray EL, Hicks CH, Goldstein RA. Congestive heart failure with normal systolic function. Am J Cardiol 1984, 54:778-82.
33. Dubus I, Samuel J-L, Swynghedauw B. Origin and mechanisms of heart fallure in hypertensive patients: left ventricular remodeling in hypertensive heart disease. Eur Heart 1993, J 14 (Suppl):76-81.
34. Skorton DJ, Vandenberg B. Ultrasound tissue characterization of the diabetic heart: laboratory curiosity or clinical tool? J Am Coll Cardiol 1992, 19:1163-4.
35. Thomson EDW. Structural manifestations of diabetic cardiomyopathy in the rat and its reversal by insulin treatment. Am J Anat 1988, 182:270-82.
36. Perez JE, McGill JB, Santiago JV, et al. Abnormal myocardial accoustic properties in diabetic patients and their correlation with the severity of disease. J Am Coll Cardiol 1992, 19:1154-62.
37. Solomon SB, Nicolic SD, Glantz SA, Yellin EL. Left ventricular diastolic function of remodeled myocardium in dogs with pacing-induced heart failure. Am J Physiol 1998, 274:945-54.
38. Feigenbaum H. Hemodynnamic information derived from echocardiography. In: Feigenbaum H (ed): Echocardiography. 4th ed, Philadelphia, Lea & Febiger, 1986, 188-229.
39. Lefkos N, Boudonas G, Vassilikos V, Efthimiadis A. Influence of left ventricular hypertrophy on the diastolic performance in hypertensive patients and in athletes. Acta Cardiologica 1993, XLVIII:507-514.
40. Feigenbaum H. Echocardiographic evaluation of cardiac chambers. In: Feigenbaum H (ed): Echocardiography. 4th ed, Philadelphia, Lea & Febiger, 1986, 127-187.

Αλληλογραφία
Δ. Ψυρρόπουλος
Ιπποκράτειο Γ.Π.Ν. Θεσσαλονίκης
Κωνσταντινουπόλεως 49
546 42 Θεσσαλονίκη

Corresponding author
Psirropoulos D,
Cardiology Unit of 2nd Dept. of
Internal Medicine
Aristotelian University
Hippokration Hospital of Thessaloniki
49, Konstantinoupoleos Str.
546 42 Thessaloniki
Greece