Journal of

Cardiology and Therapy

Online Submissions: http://www.ghrnet.org/index./jct/
doi:10.6051/j.issn.2309-6861.2015.02.43

Journal of Cardiol Ther 2015 April 2(2): 273-278
ISSN 2309-6861(print), ISSN 2312-122X(online)

EDITORIAL

Diabetic Cardiomyopathy: Current Status

João Soares Felício, Camila Cavalcante Koury, João Felício Abrahão Neto

João Soares Felício, Camila Cavalcante Koury, João Felício Abrahão Neto, Endocrinology Division, Hospital Universitário João de Barros Barreto, Universidade Federal do Pará, Rua dos Mundurucus, 4487, Guamá, Belém, Pará, Brazil

Correspondence to: João Felício Abrahão Neto, Endocrinology Division, Hospital Universitário João de Barros Barreto, Universidade Federal do Pará, Rua dos Mundurucus, 4487, Guamá, Belém, Pará, Brazil

Email: felicio.bel@terra.com.br

Telephone: +55-91-3201-6760 Fax: +55-91-3201-1329

Received: July 14, 2014 Revised: August 12, 2014

Accepted: August 16, 2014

Published online: April 10, 2015

ABSTRACT

Some clinical, epidemiological and histopathological data support the occurrence of a specific cardiomyopathy related to diabetes mellitus, independent of hypertension and coronary artery disease. The pathogenesis of diabetic cardiomyopathy is partially understood and is likely to be multifactorial, involving metabolic disturbances and autonomic neuropathy. This review discusses the possible mechanisms that may be involved in the development and progression of cardiac dysfunction in diabetes, and seeks to define the best approach to prevent and reduce the cardiovascular morbidity and mortality of diabetic cardiomyopahty.

Key words: Diabetic Cardiomyopathy; Diabetes Mellitus; Ambulatorial Blood Pressure Measurement; Diabetic Autonomic Neuropathy

Felício JS, Koury CC, Neto JFA. Diabetic Cardiomyopathy: Current Status. *Journal of Cardiology and Therapy* 2015; 2(2): 273-278 Available from: URL: http://www.ghrnet.org/index.php/jct/article/view/1150

INTRODUCTION

Some clinical, epidemiological and histopathological data support the occurrence of a specific cardiomyopathy related to diabetes mellitus (DM). However, the exact etiology of this complication remains uncertain[1-4]. Diabetes mellitus has multifactorial detrimental effects on myocardial tissue[5] and is commonly associated with hypertension and coronary atherosclerosis[6], which can singly reduce myocardial performance and increase cardiovascular mortality. Therefore, considering the numerous confounders, especially in type 2 diabetes, it is difficult to determine whether diabetic cardiomyopathy is a unique clinical entity independent of other conditions, due exclusively to the direct effects of the abnormal myocardial metabolism in diabetes.

The existence of diabetic cardiomyopathy was first suggested by Rubler *et al* in 1972, on the basis of autopsy findings in four diabetic adults with congestive heart failure in the absence of coronary, valvular, congenital and hypertensive heart disease[7]. The role of DM as a causal factor in the development of congestive heart failure was more conclusively delineated in the Framingham Heart Study, which found this condition to be more frequent in diabetic patients when compared to age-matched control subjects, independently of age, weight, office blood pressure, hypercholesterolemia and coronary artery disease[8]. Studies using independent population databases have provided similar results, revealing increased heart failure rates in subjects with diabetes mellitus in cross-sectional analyses and increased risk for developing heart failure in prospective analyses, even after correction for confounding variables[9-11].

The pathogenesis of diabetic cardiomyopathy is partially understood and is likely to be multifactorial, involving complex cellular and molecular perturbations that predispose to altered myocardial structure and function. Some appealing hypotheses to explain the development of this condition have been proposed, and include metabolic disturbances (hyperglycemia, hyperinsulinemia and abnormalities in myocardial lipid metabolism) and autonomic neuropathy (AN)[1,12-14].

CARDIAC PRECLINICAL DAMAGE

Diabetic cardiomyopathy is a distinct entity diagnosed when ventricular dysfunction develops in patients with diabetes in the absence of coronary atherosclerosis and hypertension[15-18]. The most commonly observed cardiac abnormalities in clinical studies of asymptomatic diabetics include diastolic cardiac dysfunction and left ventricular hypertrophy, which configure preclinical abnormalities[9, 19-21].

In regard to the clinical evaluation of the preclinical abnormalities of diabetic cardiomyopathy, it is noteworthy that the diastolic function parameters (peak flow velocity of early left ventricular filling, peak flow velocity of late left ventricular filling, early deceleration time, isovolumetric relaxation period and the ratio between early and late diastolic flow velocity peaks) are useful in population studies, but present significant individual variability. Additionally, despite the excellent reliability of echocardiography for measurement of left ventricular mass (intraclass coefficient of correlation 0.86), the 95% confidence interval (CI) width of a single replicate measurement of left ventricular mass is 59 grams, exceeding usual decreases in mass during treatment. However, within a population, the CI decreases proportionally with the inverse of the square root of the sample size, which makes it possible to evaluate decreases and increases in LVMI in large groups[22].

Left ventricular diastolic dysfunction has been widely reported in diabetic animals[23,24] and diabetic patients without evidence of heart disease caused by other factors[25]. Studies of well-controlled type 2 diabetic subjects without clinically detectable heart disease showed that 52 to 60% of them had diastolic dysfunction[26,27]. Abnormal diastolic inflow patterns reflect underlying disorders in relaxation and/or reduced myocardial compliance, associated with myocardial fibrosis[28]. Echocardiographic changes consistent with left ventricular hypertrophy (LVH) have been described in a number of studies of diabetic populations and may portend an increased risk for the subsequent development of heart failure, particularly in the presence of coexisting hypertension[29-33]. In the Framingham Heart study, diabetic women had a left ventricular mass index (LVMI) 10% greater than the nondiabetic patients[32].

Additionally, left ventricular hypertrophy and cardiac diastolic dysfunction are more frequent and more likely to become clinically apparent in diabetic patients when associated with hypertension, suggesting a maximization of damage on the myocardium in the presence of both DM and hypertension[19,34,35]. Grossman *et al*[36] showed that hypertensive patients with DM, when compared to essential hypertensive patients, had a higher LVMI independent of office blood pressure. However, this study did not evaluate the blood pressure rhythm in 24 hours. Studying 91 hypertensive patients with type 2 DM, 59 nondiabetic hypertensive patients and 26 healthy control subjects with Ambulatorial Blood Pressure Measurement (ABPM) and echocardiography with Doppler, we demonstrated that diabetic patients presented higher nocturnal systolic blood pressure (NSBP) and increased LVMI. These findings occurred independently of sex, age, body mass index and diurnal blood pressure levels. Patients with DM also presented a worse diastolic function (early deceleration time and peak flow velocity of late left ventricular filling) when compared to nondiabetic hypertensive patients[37].

Additionally, Di Bello *et al* using ultrasound cardiac tissue characterization with backscatter analysis, demonstrated increased myocardial echodensity, possibly related to interstitial collagen deposition, in asymptomatic type 1 diabetic patients with normal rest function. Theoretically, this finding might be considered a very early preclinical alteration, potentially related to subsequent development of diabetic cardiomyopathy[38].

ROLE OF HYPERGLYCEMIA

The severity and duration of hyperglycemia has been shown to directly parallel the incidence of diabetic cardiomyopathy in patients with diabetes[39]. We were the first ones to demonstrate, in 2000, that the improvement of glycemic control in type 2 diabetic patients per se is capable of reverting left ventricular hypertrophy. The reduction of 10% in LVMI was associated with a fasting blood glucose reduction from 178±36 to 147±30 mg/dL ($p<0.01$) and a correlation was observed between blood glucose and LVMI percent variations ($r=0.5$, $p<0.01$). These results occurred independently of blood pressure and cholesterol levels, in diabetics without coronary artery disease. However, we didn't perform ABPM in these patients. The better glycemic control could be responsible for a reduction of nocturnal blood pressure levels, which could explain the improvement of the left ventricular mass index. Thus, the glycemic control would have an indirect effect on the left ventricular hypertrophy[40].

Furthermore, we found that diabetics with nocturnal systolic blood pressure greater than 140 mmHg and elevated fasting blood glucose levels showed an additional risk of LVH ($p<0.05$; odds ratio=11) (Figure 1)[37].

A few short-term studies have shown that systolic left ventricular function may improve if hyperglycemia is corrected[41,42]. However, the abnormalities in diastolic cardiac function are considered to be largely irreversible[14,43]. Accordingly, in our study, there were no important changes in left ventricular diastolic function when glycemic control was improved[40].

Other authors argue that hyperglycemia could be one of the main responsible for the damage caused by diabetes on the myocardium[12,44]. Barbagallo *et al*[12] performed a multivariate regression, which indicated that the contribution of glucose levels to LVMI was independent of age, body mass index, fasting insulin levels and blood pressure, and demonstrated a significant interaction with intracellular calcium (Cai). Altogether, these data suggest that

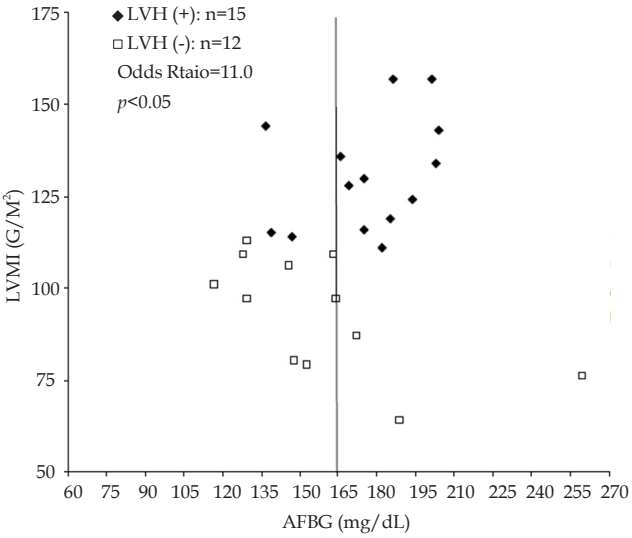

Figure 1 Risk of left ventricular hypertrophy and average of fasting blood glucose values in patients with nocturnal systolic blood pressure greater than140 mmHg. LVMI=left ventricular mass index; AFBG=average of fasting blood glucose; LVH=left ventricular hypertrophy.

glucose-related excess Cai is a fundamental lesion in diabetes that contributes to the elevated blood pressure and cardiac mass in this disease.

Furthermore, sustained hyperglycemia may increase glycation of interstitial proteins such as collagen, resulting in myocardial stiffness and impaired contractility[45-47]. The myocardial content of free radicals and oxidants is also increased by high blood glucose levels, which leads to decreased nitric oxide levels, worse endothelial function, and induces myocardial inflammation through stimulation of poly(ADP-ribose) polymerase-1[48].

Increasing evidence demonstrates that advanced glycation end products (AGEs) play a pivotal role in the development and progression of diabetic heart failure. AGEs are generated intra- and extracellularly as a result of chronic hyperglycemia, and once formed, they are irreversible. Then, following the interaction with receptors for advanced glycation end products (RAGEs), a series of events leading to vascular and myocardial damage are elicited and sustained, which include oxidative stress, increased inflammation, and enhanced extracellular matrix accumulation resulting in diastolic and systolic dysfunction[49-51].

A recent review on diabetes and cardiovascular disease showed the role of an intensive glycemic control in the reduction of mortality rates and risk of complications after an acute myocardial infarction or cardiac surgery in diabetic patients[52]. These clinical data sustain the fact that glucose levels are critical to myocardial damage in diabetic patients; however the mechanism responsible for this injury is not completely elucidated yet.

ROLE OF DIABETIC AUTONOMIC NEUROPATHY AND ABSENCE OR REDUCTION OF BLOOD PRESSURE DESCENT DURING SLEEP

Diabetic autonomic neuropathy, characterized by denervation and alterations in myocardial catecholamine levels, has been associated with a high cardiac mortality rate[53,54]. Cardiovascular autonomic neuropathy (CAN) is an independent risk factor for cardiovascular mortality and silent myocardial ischemia[55,56]. Histological evidence of AN has been found in diabetic patients with painless myocardial infarction[57] and autopsy studies have found low concentrations of noradrenalin in diabetic patients with cardiomyopathy[58]. Kahn *et al*[59], comparing diabetics with and without AN, found that the former had reduced levels of plasma catecholamines and that this finding was related to abnormalities in diastolic cardiac function. Sympathetic stimulation not only increases the contractility of the left ventricle but also increases their rate of relaxation[19].

In early stages, CAN may be completely asymptomatic and detected by changes in heart rate variability and abnormal cardiovascular reflex tests (R-R response to deep breathing, standing and Valsalva maneuver). Advanced disease may be indicated by resting tachycardia (>100 bpm) and orthostasis (a fall in systolic boold pressure >20 mmHg or diastolic blood pressure of at least 10 mmHg upon standing without an appropriate heart rate response). The standard cardiovascular reflex testing, especially the deep breathing test, is noninvasive, easy to perform, reliable, reproducible and has prognostic value[60].

The main determinant of the blood pressure circadian pattern appears to be the sympathetic nervous system and DM has been associated with elevated levels of nocturnal blood pressure[61]. It has been suggested that poor metabolic control could be the mechanism responsible for this elevation[62]. Increased nocturnal blood pressure has been described in diabetic autonomic neuropathy, diabetic nephropathy, essential hypertensive patients with chronic renal failure, malignant hypertension and essential hypertensive patients without other associated pathology[61,63,64]. AN could reduce nocturnal decline of blood pressure by reducing vagal tone and a consequent increase in cardiac output during sleep[61,65,66], which has been associated with a higher risk of cardiovascular complications[67,68]. Ambulatory blood pressure monitoring can be particularly useful in detecting absence or reduction of blood pressure descent during sleep[69]. We assessed the reproducibility of ABPM measurements and the placebo effect on ABPM to determine its degree of reliability as to the measurement of pressure levels in patients with type 2 DM and hypertension. The results of our study showed that mean pressure values assessed by ambulatory blood pressure monitoring presented good reproducibility and were not affected by placebo (Figure 2)[70]. These findings are similar to few data found in the literature[71,72].

We have also demonstrated a correlation of AN tests with LVMI and cardiac diastolic function (CDF) in normotensive patients with DM2. Positive AN tests occurred even before LVH, impaired CDF and diabetic AN symptoms were present. This correlation was not found in the control group. Additionally, in diabetic individuals, AN tests were correlated with average glycated hemoglobin. Our data suggested that AN could precede LVH and be a contributing factor to preclinical cardiac abnormalities in normotensive patients with DM2. Thus, we recommend that AN tests should be regularly performed in patients with DM2, and that any abnormalities in those tests should be followed by a detailed cardiac evaluation[73].

Additionally, we have found that hypertensive patients with type 2 DM when compared to patients with essential hypertension presented higher nocturnal systolic blood pressure (NSBP), higher LVMI and worse CDF. These findings occurred independently of sex, age, body mass index and diurnal blood pressure levels[37].

These data reinforce the hypothesis that AN could be a via through which hyperglycemia could increase nocturnal blood pressure and lead to diabetic cardiomyopathy.

Furthermore, we have also demonstrated that the absence or reduction of blood pressure descent during sleep is also associated with other microvascular complications in patients with type 2 DM, such as diabetic retinopathy and nephropathy. Our study showed that diabetic patients with retinopathy had higher NSBP levels than

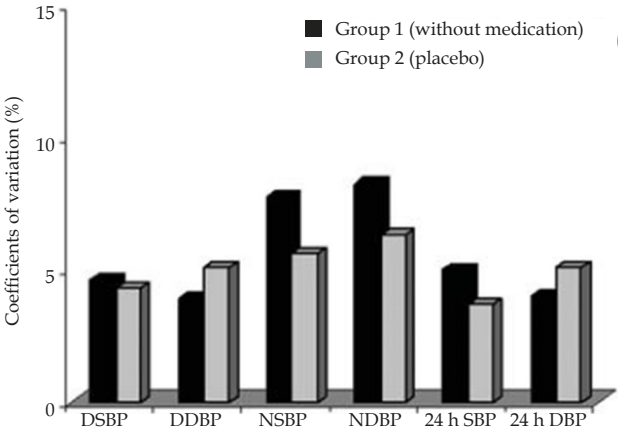

Figure 2 Coefficients of variation of pressure measurements determined by ABPM. DSBP=Systolic BP during alertness; DDBP=Diastolic BP during alertness; NSBP=Systolic BP during sleep; NDBP=Diastolic BP during sleep; 24hSBP=24-hour systolic BP; 24hDBP=24-hour diastolic BP.

diabetic patients without retinopathy, independent of diurnal blood pressure, age, sex, duration of DM and body mass index. This result was confirmed by multivariate regression analysis, in which NSBP was an independent predictor of diabetic retinopathy[74]. In regard to diabetic nephropathy, we demonstrated in a prospective study that an elevation of nocturnal systolic blood pressure and a loss of nocturnal blood pressure fall might precede the onset of abnormal albuminuria and cardiovascular events in hypertensive normoalbuminuric patients with type 2 diabetes[75].

CONCLUSION

Since diabetic cardiomyopathy is known to have a high prevalence in the asymptomatic type 2 diabetic patient, screening for its presence at the earliest stage of development would be appropriate in order to prevent the progression to congestive heart failure.

Therefore, we suggest that all type 2 diabetic patients should be evaluated by ABPM and echocardiography to identify loss of nocturnal blood pressure fall and preclinical cardiac abnormalities (cardiac diastolic dysfunction and LVH), respectively. Once identified these conditions, an intensive control of 24-hour blood pressure (especially during the night) and hyperglycemia must be achieved. This approach could have a significant impact in the prevention of diabetic cardiomyopathy and reduce cardiovascular morbidity and mortality in these patients.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

REFERENCES

1. Fein FS, Sonnenblick EH. Diabetic cardiomyophaty. *Prog Cardiovasc Dis* 1985; **27**: 255-270
2. Regan TJ. Congestive heart failure in the diabetic. *Annu Rev Med* 1983; **34**: 161-168
3. Blumenthal HT, Alex M, Goldenberg S. A study of lesions of the intramural coronary artery branches in diabetes mellitus. *Arch Pathol* 1960; **70**: 13-28
4. Ledet T. Histological and histochemical changes in the coronary arteries of old diabetic patients. *Diabetologia* 1968; **4**: 268-272
5. Torella D, Ellison GM, Torella M, Vicinanza C, Aquila I, Iaconetti C, Scalise M, Marino F, Henning BJ, Lewis FC, Gareri C, Lascar N, Cuda G, Salvatore T, Nappi G, Indolfi C, Torella R, Cozzolino D, Sasso FC. Carbonic Anhydrase Activation Is Associated With Worsened Pathological Remodeling in Human Ischemic Diabetic Cardiomyopathy. *J Am Heart Assoc* 2014; **3**: e000434
6. Garcia MJ, McNamara PM, Gordon T, Kannell WB. Morbidity and mortality in diabetics in the Framingham population: sixteen year follow-up study. *Diabetes* 1974; **23**: 105-111
7. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A. New type of cardiomyophaty associated with diabetic glomeruloesclerosis. *Am J Cardiol* 1972; **30**: 595-602
8. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol* 1974; **34**: 29-34
9. Bertoni AG, Tsai A, Kasper EK, Brancati FL. Diabetes and idiopathic cardiomyopathy: a nationwide case-control study. *Diabetes Care* 2003; **26**: 2791-2795
10. Nichols GA, Hillier TA, Erbey JR, Brown JB. Congestive heart failure in type 2 diabetes: prevalence, incidence, and risk factors. *Diabetes Care* 2001; **24**: 1614 -1619
11. Aronow WS, Ahn C. Incidence of heart failure in 2,737 older persons with and without diabetes mellitus. *Chest* 1999; **115**: 867-868
12. Barbagallo M, Grupta R, Resnick L. Cellular ions in NIDDM: Relation of calcium to hyperglycemia and cardiac mass. *Diabetes Care* 1996; **19**: 1393-1398
13. Paulson DJ, Crass MF. Myocardial triacyglycerol fatty acid composition in diabetes mellitus. *Life Sci* 1980; **27**: 2237-2243
14. Uusitupa M, Mustonen J, Airaksinen J. Diabetic heart muscle disease. *Ann Med* 1990; **22**: 377-386
15. Francis GS. Diabetic cardiomyopathy: fact or fiction? *Heart* 2001; **85**: 247-248
16. Picano E. Diabetic cardiomyopathy. The importance of being earliest. *J Am Coll Cardiol* 2003; **42**: 454-457
17. Avogaro A, Vigili dKS, Negut C, Tiengo A, Scognamiglio R. Diabetic cardiomyopathy: a metabolic perspective. *Am J Cardiol* 2004; **93**: 13A-16A
18. Adeghate E. Molecular and cellular basis of the aetiology and management of diabetic cardiomyopathy: a short review. Mol Cell Biochem 2004; **261**: 187-191
19. Kahn CR, Weir GC. Joslin's diabetes mellitus. 13th ed. Pennsylvania: Lea and Febige, 1994: 836-851
20. Rutter MK, Parise H, Benjamin EJ, Levy D, Larson MG, Meigs JB, Nesto RW, Wilson PW, Vasan RS. Impact of glucose intolerance and insulin resistance on cardiac structure and function: sex-related differences in the Framingham Heart Study. *Circulation* 2003; **107**: 448-454
21. Tenenbaum A, Fisman EZ, Schwammenthal E, Adler Y, Benderly M, Motro M, Shemesh J. Increased prevalence of left ventricular hypertrophy in hypertensive women with type 2 diabetes mellitus. *Cardiovasc Diabetol* 2003; **2**: 14
22. Gottdiener JS, Chase GA. Should echocardiography be performed to assess effects of antihypertensive therapy? Test-retest reliability of echocardiography for measurement of left ventricular mass and function. *J Am Coll Cardiol* 1995; **25**: 424-430
23. 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
24. Ganguly PK, Thliveris JA, Mehta A. Evidence against the involvement of nonenzymatic glycosylation in diabetic cardiomyopathy. Metabolism 1990; **39**: 769-773
25. Fang ZY, Prins JB, Marwick TH. Diabetic Cardiomyopathy: Evidence, Mechanisms, and Therapeutic Implications. *Endocrine Reviews* 2004; **25**: 543-567
26. Redfield MM, Jcobsen SJ, Burnett JC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community. *JAMA* 2003; **289**: 194-202
27. 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
28. Shehadeh A, Regan TJ. Cardiac consequences of diabetes mellitus. *Clin Cardiol* 1995; **18**: 301-305
29. Bella JN, Devereux RB, Roman MJ, Palmieri V, Liu JE, Paranicas M, Welty TK, Lee ET, Fabsitz RR, Howard BV. Separate and joint effects of systemic hypertension and diabetes mellitus on left ventricular structure and function in American Indians (the Strong Heart Study). *Am J Cardiol* 2001; **87**: 1260-1265
30. Ilercil A, Devereux RB, Roman MJ, Paranicas M, O'Grady MJ, Welty TK, Robbins DC, Fabsitz RR, Howard BV, Lee ET. Relationship of impaired glucose tolerance to left ventricular structure and function: the Strong Heart Study. *Am Heart J* 2001; **141**: 992-998
31. 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**: 2271-2276
32. Galderisi M, Anderson KM, Wilson PW, Levy D. Echocardiographic evidence for the existence of a distinct diabetic cardiomy-

opathy (the Framingham Heart Study). *Am J Cardiol* 1991; **68**: 85-89
33. Struthers AD, Morris AD. Screening for and treating left-ventricular abnormalities in diabetes mellitus: a new way of reducing cardiac deaths. *Lancet* 2002; **359**: 1430-1432
34. Bell DSH. Diabetic cardiomyopathy: a unique entity or a complication of coronary artery disease? *Diabetes Care* 1995; **18**: 708-714
35. Factor SM, Minase T, Sonnenblick EH: Clinical and morphological features of human hypertensive-diabetic cardiomyophaty. *Am Heart J* 1980; **99**: 446-58
36. Grossman E, Shemesh J, Shamiss A, Thaler M, Carroll J, Rosenthal T. Left ventricular mass in diabetes-hypertension. *Arch Int Med* 1992; **152**: 1001-1004
37. Felício JS, Pacheco JT, Ferreira SR, Plavnik F, Moisés VA, Kohlmann Jr O, Ribeiro AB, Zanella MT. Hyperglycemia and nocturnal systolic blood pressure are associated with left ventricular hypertrophy and diastolic dysfunction in hypertensive diabetic patients. *Cardiovascular Diabetology* 2006; **5**: 19
38. Di Bello V, Talarico L, Picano E, Di Muro C, Landini L, Paterni M. Increased Echodensity of Myocardial Wall in the Diabetic Heart: An Ultrasound Tissue Characterization Study. *J Am Coil Cardiol* 1995; **25**: 1408-1415
39. Poornima I, Parikh P, Shannon R. Diabetic Cardiomyopathy: The search for a unifying hypothesis. *Circulation Research* 2006; **98**: 596-605
40. Felício JS, Ferreira SR, Plavnik FL, Moisés V, Kohlmann Jr O, Ribeiro AB, Zanella MT. Effect of blood glucose on left ventricular mass in patients with hypertension and type 2 diabetes mellitus. *Am J Hypertens* 2000; **13**:1149-1154
41. Uusitupa M, Siitonen O, Aro A, Korhonen T, Pyörälä K. Effect of correction of hyperglycemia on left ventricular function in non-insulin-dependent (type 2) diabetics. *Acta Med Scand* 1983; **213**: 363-368
42. Mustonen J, Laakso M, Uusitupa M, Sarlund H, Pyörälä K, Rautio P, Kuikka J, Länsimies E. Improvement of left ventricular function after starting insulin treatment in patients with non-insulin-dependent diabetes. *Diabetes Res* 1988; **9**: 27-30
43. Fein FS. Diabetic cardiomyophaty. *Diabetes Care* 1990; **13**: 1169-1179
44. Resnick LM, Barbagallo M, Gupta RK, Laragh JH. Ionic basis of hypertension in diabetes mellitus: role of hyperglycemia. *Am J Hypertens* 1993; **6**: 413-417
45. Avendano GF, Agarwal RK, Bashey RI, Lyons MM, Soni BJ, Jyothirmayi GN, Regan TJ. Effects of glucose intolerance on myocardial function and collagen-linked glycation. *Diabetes* 1999; **48**: 1443-1447
46. Capasso JM, Robinson TF, Anversa P. Alterations in collagen crosslinking impair myocardial contractility in the mouse heart. *Circ Res* 1989; **65**: 1657-1664
47. Berg TJ, Snorgaard O, Faber J, Torjesen PA, Hildebrandt P, Mehlsen J, Hanssen KF. Serum levels of advanced glycation end products are associated with left ventricular diastolic function in patients with type 1 diabetes. *Diabetes Care* 1999; **22**: 1186-1190
48. Szabo C. PARP as a drug target for the therapy of diabetic cardiovascular dysfunction. *Drug News Perspect* 2002; **15**: 197–205
49. Bakris GL, Bank AJ, Kass DA, Neutel JM, Preston RA, Oparil S (review). Advanced glycation end-product cross-link breakers. A novel approach to cardiovascular pathologies related to the aging process. *Am J Hypertens* 2004; **17**: 23S-30S
50. Goldin A, Beckman J, Schmidt AM, Creager M. Advanced Glycation End Products Sparking the Development of Diabetic Vascular Injury. *Circulation* 2006; **114**: 597-605
51. Bodiga VL, Eda SR, Bodifa S. Advanced glycation end products: role in pathology of diabetic cardiomyopathy. *Heart Fail Rev* 2014; **19**: 49-63
52. Bertoluci MC, Pimazoni-Netto A, Pires AC, Pesaro AE, Schaan BD, Caramelli B, Polanczyk CA, Serrano Júnior CV, Gualandro DM, Malerbi DA, Moriguchi E, Borelli FAO, Salles JEN, Mariani Júnior J, Rohde LE, Canani LH, Cesar LAM, Tambascia M, Zanella MT, Gus M, Scheffel RS, Santos RS. Diabetes and cardiovascular disease: from evidence to clinical practice – position statement 2014 of Brazilian Diabetes Society. *Diabetology & Metabolic Syndrome* 2014; **6**: 58
53. Ewing DJ, Campbell IW, Clarke BF. The natural history of diabetic autonomic neuropathy. *QJ Med* 1980; **49**: 95-108
54. Ewing DJ, Campbell IW, Clarke BF. Assessment of cardiovascular effects in diabetic autonomic neuropathy and prognostic implications. *Ann Intern Med* 1980; **92**: 308-311
55. Pop-Busui R, Evans GW, Gerstein HC, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Diabetes Care* 2010; **33**: 1578-1584
56. Spallone V, Ziegler D, Freeman R, et al.; Toronto Consensus Panel on Diabetic Neuropathy. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. *Diabetes Metab Res Rev* 2011; **27**: 639-653
57. Faerman I, Faccio E, Milei J, et al. Autonomic neuropathy and painless myocardial infarction in diabetic patients: histologic evidence of their relationship. *Diabetes* 1977; **6**: 1147-1158
58. Neubauer B, Christensen NJ. Norepinephrine, epinephrine and dopamine content of the cardiovascular system in long-term diabetics. *Diabetes* 1976; 25: 6-10
59. Kahn JK, Zola B, Juni JE, Vinik AL. Radionuclide assessment of left ventricular diastolic filling in diabetes mellitus with and without cardiac autonomic neuropathy. *J Am Coll Cardiol* 1986; **7**: 1303-1309
60. American Diabetes Association. Standards of medical care in diabetes – 2014. *Diabetes Care* 2014; **37(Suppl 1)**: S14-80
61. Spallone V, Gambardella S, Maiello MR, Barini A, Frontoni S, Menzinger G. Relationship between autonomic neuropahty, 24-h blood pressure profile, and nephropathy in normotensive IDDM patients. *Diabetes Care* 1994; **17**: 578-584
62. Hansen KW, Pedersen MM, Marshal SM, Christiansen JS, Mogensen CE. Circadian variation of blood pressure in patients with diabetic nephropathy. *Diabetologia* 1992; **35**: 1074-1079
63. Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Guerrieri M, Gatteschi C, Zampi I, Santucci A, Santucci C, Reboldi G. Ambulatory blood pressure: An Independent Predictor of prognosis in essential hypertension. *Hypertension* 1994; **24**: 793-801
64. Schleiffer T, Klooker P, Brass H. 24-h blood pressure measurament in type II diabetic patients with and without nephropathy. *Z Kardiol* 1992; **81**: 75-78
65. Mann S, Altman DG, Raftery EB, Bannister R. Circadian variation of blood pressure in autonomic failure. *Circulation* 1983; **68**: 477-483
66. Mulec H, Blohme G, Kullenberg K, Nyberg G, Björck S. Latent overhydration and nocturnal hypertension in diabetic neprhopathy. *Diabetologiac* 1995; **38**: 216-220
67. Manning G, Rushton L, Donnelly R, Millar-Craig MW. Variability of diurnal changes in ambulatory blood pressure and nocturnal dipping status in untreated hypertensive and normotensive subjects. *Am J Hypertens* 2000; **13**:1035-1038
68. Cuspidi C, Meani S, Salerno M, Valerio C, Fusi V, Severgnini B. Reproducibility of nocturnal blood pressure fall in early phases of untreated essential hypertension: a prospective observational study. *J Hum Hypertens* 2004; **18**: 503-509
69. Bezdah L, Ouerdiane D, Kamoun M, Abid N, Lamine F, Kasri R. Value of ambulatory blood pressure monitoring in blood pressure profile determination in type 2 diabetes. *Tunis Med* 2002; **80**: 769-774
70. Felício JS, Pacheco JT, Ferreira SR, Plavnik F, Kohlmann O,

Ribeiro AB, Zanella MT. Reproducibility of Ambulatory Blood Pressure Monitoring in Hypertensive Patients with Type 2 Diabetes Mellitus. *Arq Bras Cardiol* 2007; **88**: 183-186
71. Nielsen F, Rossing P, Bang L, Svendsen TL, Gall MA, Smidt UM. On the mechanisms of blunted nocturnal decline in arterial blood pressure in NIDDM patients with diabetic nephropathy. *Diabetes* 1995; **44**: 783-789
72. Prisant LM, Bottini P, Carr AA. Ambulatory blood pressure monitoring: methodologic issues. *Am J Nephrol* 1996; **16**: 190-201
73. Felício JS, Santos FM, Souza ACCB, Felício KM, Ribeiro AB, Zanella MT. Autonomic neuropathy tests correlate with left ventricular mass and cardiac diastolic function in normotensive patients with type 2 diabetes mellitus and without left ventricular hypertrophy. *Exp Clin Cardiol* 2010; **15**: e5-e9
74. Felício JS, Pacheco JT, Ferreira SR, Plavnik F, Moisés V, Kohlmann Jr O, Ribeiro AB, Zanella MT. Impaired reduction of nocturnal systolic blood pressure and severity of diabetic retinopathy. *Exp Clin Cardiol* 2007; **12**: 157-160
75. Felício JS, Souza ACCB, Kolmann N, Kohlmann Jr O, Ribeiro AB, Zanella MT. Nocturnal blood pressure fall as predictor of diabetic nephropathy in hypertensive patients with type 2 diabetes. *Cardiovascular Diabetology* 2010; **9**: 36

Peer reviewers: Jun LU, Faculty of Health & Environmental Sciences, Auckland University of Technology, Private Bag 92006, Box A-25, Auckland 1142, New Zealand; Juei-Tang Cheng, PhD, FCP, Graduate School of Medical Sciences, Chang Jung Christian University, Quei-Ren, Tainan City, Taiwan.