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Both ramipril and telmisartan reverse indices of early diabetic cardiomyopathy: A comparative study

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Abstract *Aims:* We tested the hypothesis that renin—angiotensin system inhibition could reverse left ventricular diastolic dysfunction in patients with type 2 diabetes.

Methods and results: Forty asymptomatic patients with type 2 diabetes were recruited in this double-blind cross-over trial. Left ventricular diastolic function was assessed at baseline with Doppler echocardiography; ratios of early to late peak flow velocity through the mitral orifice (E/A) and velocity time integral of early to late transmitral diastolic flow (VTIE/VTIA) were evaluated. In addition, plasma brain natriuretic peptide (BNP) was measured.

Patients received randomly either ramipril (2.5 mg/day), or telmisartan (40 mg/day) or their combination for 3 months. Subsequently, every patient was crossed over to alternative regimens after a 2-week washout period. Measurements were repeated at the end of each treatment period.

Both E/A and VTIE/VTIA ratios were increased (29 and 20% with ramipril, 25 and 23% with telmisartan and 36 and 28% with combination treatment, respectively, $p < 0.001$), whereas plasma BNP levels were significantly reduced with all 3 regimens (9% with ramipril, 25% with telmisartan and 36% with combination, $p < 0.001$).

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Conclusions: Both ramipril and telmisartan improve echocardiographic left ventricular diastolic indices and reduce plasma BNP levels in diabetic patients; their combination yields an even better therapeutic effect.

Introduction

Diabetic cardiomyopathy (DCM) is a distinct clinical entity of the diabetic heart muscle, independent of hypertension or coronary artery disease (CAD) that presents as diastolic and/or systolic dysfunction. Left ventricular diastolic dysfunction (LVDD) is a common finding in both diabetic animals[1,2] and diabetic patients,[3–6] without any other apparent reason for heart muscle disease and seems to precede systolic dysfunction.[7,8]

Angiotensin converting enzyme (ACE) inhibitors have a well-established role in the treatment of arterial hypertension, left ventricular hypertrophy, coronary artery disease, heart failure, endothelial dysfunction diabetic nephropathy and insulin resistance.[9–13] On the other hand, angiotensin receptor blockers (ARBs) have emerged as a promising new treatment modality. Angiotensin II has been shown to promote myocardial fibrosis, myocyte apoptosis and hypertrophy, structural and functional vascular abnormalities, endothelial dysfunction, inflammation, increased insulin resistance and oxidative stress, factors that have all been implicated as possible mechanisms for the development of DCM.[14] Therefore, the interruption of the RAS by an ACE-inhibitor and/or an ARB could retard or even regress the progression of DCM. However, direct comparisons between these two drug categories, as well as a possible additive effect of the combination treatment regarding cardioprotective properties have been scarce.

Thus, we conducted this clinical trial in order to assess and compare the efficacy of ramipril (an ACE-inhibitor) and telmisartan (an ARB) in improving left ventricular diastolic properties in a diabetic population.

Methods

Study population

Forty patients (17 men and 23 women) with type 2 diabetes were recruited in this trial. Their baseline characteristics are shown in Table 1. No patient had a history of hypertension, congestive heart failure (CHF), impaired left ventricular systolic function, left ventricular hypertrophy, significant valvulopathy or CAD. They all had relatively well-controlled diabetes (glycated hemoglobin $< 8\%$) and a negative stress test. All subjects were free of diabetic complications, such as neuropathy, macro-angiopathy (peripheral arterial disease or history of prior cerebrovascular episode) and nephropathy (renal failure and microalbuminuria). Patients should abstain from ACE-inhibitors or ARBs for at least 6 months prior to the beginning of the study. Moreover, other antihypertensive medications and statins were not allowed throughout the duration of the trial.

Study protocol

The study was designed as a randomized double-blind cross-over trial. A detailed medical history was obtained and a complete physical examination and an electrocardiogram were done at baseline. A follow-up visit for clinical evaluation and a repeat electrocardiogram was performed at each month. Patients had a baseline assessment of serum biochemical markers and left ventricular diastolic indices. All subjects randomly received ramipril 2.5 mg/day or telmisartan 40 mg/day or their combination for 3 months. Subsequently, they were crossed over to alternative regimens by random order. Blood draws and ultrasound Doppler recordings were repeated at the end of each treatment trimester (i.e. 3, 6 and 9 months). All participants gave a written informed

Table 1 Baseline clinical characteristics of study patients ($n = 40$)

Age (years)	53.2 ± 11.9
Men/women	17/23
Body mass index (kg/m^2)	27.7 ± 3.3
Waist to hip ratio	0.9 ± 0.07
Duration of diabetes (years)	8.1 ± 6.2
Drug controlled diabetes	70%
Insulin treatment	14%
Smokers	22%
Systolic blood pressure (mmHg)	116 ± 14
Diastolic blood pressure (mmHg)	75 ± 5

Values are expressed as numbers of patients (percent) or means $\pm$ SDs.

consent and our institutional research board approved the protocol.

Echocardiography

All patients had a baseline echocardiogram examination with a commercially available ultrasound system (Sonos 2500, Hewlett Packard, Andover, MA). All measurements were obtained by the same operator, who was blinded to the treatment arm of every subject, during the same hour of the day — midday — to avoid possible bias and according to the recommendations of the American Society of Echocardiography.[15] In order to evaluate the presence of LVDD and classify the transmitral flow patterns as normal, impaired relaxation, pseudonormal or restrictive the diagnostic criteria published by the Canadian consensus on diastolic dysfunction by echocardiography were used.[16] All subjects were examined in the left lateral decubitus position and by using the standard four-chamber view the following measurements were carried out: peak early transmitral filling velocity (E) and peak transmitral atrial filling velocity (A) during early and late diastole, respectively, in centimeters per second. The velocity time integral of early and late transmitral diastolic flow, in centimeters, was also obtained. All measurements were assessed at end expiration and during phase II of the Valsalva maneuver. Three consecutive cycles were studied and their average was calculated. From the same view, the right upper pulmonary vein flow was used to distinguish between normal and pseudonormal transmitral pattern.[17]

During the examination all subjects were carefully screened to exclude wall motion abnormality, significant valvulopathy, left ventricular hypertrophy or dilation, pulmonary hypertension or pericardial disease.

Biochemical measurements

At baseline and at the end of every therapeutic trimester blood samples were taken to measure several biochemical markers. Total and HDL cholesterol, as well as triglycerides were measured by using conventional enzymatic methods and plasma glucose was measured with the glucose oxidase method (Roche Diagnostics GmbH, Mannheim, Germany). The calculation of LDL-cholesterol was done in accordance to the Friedwald formula. Glycated hemoglobin A1 was assessed by high-resolution liquid chromatography (A. Menarini Diagnostics, Florence, Italy). Plasma BNP was assessed by a commercially available kit (MEIA, Abbott, USA).

Statistical analysis

Statistical analysis was performed with the use of SPSS 10.0 for Windows statistical package (SPSS Inc. 1999, Evanston, IL, USA). Data are presented as mean $\pm$ SD for continuous variables and as a percentage of patients with a characteristic for categorical variables. All variables were tested for normality with the use of Lilliefor's test. Student's *t*-test or Wilcoxon's paired test was used for comparisons between continuous variables depending on normality of distribution. Comparisons among groups were performed with one sample repeated measures analysis of variance for variables with normal distribution and with Friedman's test for variables without normal distribution. A *p*-value of <0.05 was considered statistically significant.

Results

A significant drop in systolic blood pressure ($>$20 mmHg) associated with dizziness was noted in 2 patients; one while receiving ramipril and the other while on combination regimen. They did not complete the study and were excluded from the subsequent analysis. No reduction in blood pressure was noted among the rest of the participants throughout the study, apart from an insignificant drop of 3.3 ± 3.2 mmHg in systolic blood pressure with combination therapy. Three patients experienced cough with ramipril (7.5%) and one of them had to discontinue medication. The remaining 37 patients completed the study without significant adverse effects. Lipid profile parameters did not change with treatments. The only exception to that was a significant reduction (7%) of apolipoprotein A-I levels associated with the combined ramipril and telmisartan intake in comparison to baseline values ($p = 0.018$). Left ventricular ejection fraction, plasma glucose levels, glycated hemoglobin, renal function tests and microalbuminuria remained essentially unaffected during the trial.

Table 1 shows the clinical characteristics of all 40 patients, at the beginning of the study. Table 3 shows the clinical characteristics and the values of some basic biochemical parameters of the subjects according to their classification on the diastolic function at baseline. Twenty-five patients (62.5%) had an impaired relaxation pattern and the rest 15 patients (37.5%) had a normal pattern of LV filling. No subject had a pseudonormal or a restrictive pattern. In comparison with patients with normal diastolic function, patients diagnosed with diastolic dysfunction were older (58.1 ± 7 vs

Table 2 Results

	E/A	VTIE/VTIA	BNP (pg/ml)
Baseline	0.84 ± 0.06	0.92 ± 0.09	27.8 ± 21
Ramipril	1.09 ± 0.28	1.10 ± 0.21	25.2 ± 19.9
Telmisartan	1.05 ± 0.15	1.13 ± 0.24	20.8 ± 19.5
Combination therapy	1.15 ± 0.22	1.18 ± 0.35	17.9 ± 12.9
p-Value	*<0.001*	*<0.001*	*<0.001*

None of the above regimens affected blood pressure or blood glucose levels in our patients.

51.3 ± 10 years old, $p = 0.027$), had a greater diabetes duration (9.5 ± 4.8 vs 6.6 ± 4.7 years, $p = 0.097$) and higher plasma BNP concentration (29.4 ± 18 vs 15.8 ± 9.3, $p = 0.038$). On the contrary, there were no differences between the 2 groups in systolic, diastolic and mean blood pressure, BMI index and waist to hip ratio, fasting blood glucose, glycated hemoglobin levels, lipid profile and albumin excretion rate.

All three regimens improved echocardiographic indices of left ventricular diastolic function. In particular, there was a 29% increase in E/A ratio with ramipril, 25% with telmisartan and 36% with combination treatment, in comparison with baseline ($p < 0.001$). Moreover, a 20% increase in VTIE/VTIA ratio was noted with ramipril, 23% with telmisartan and 28% with their combination ($p < 0.001$). The prevalence of LVDD declined to 50% after 3 months of treatment with ramipril, 43% after 3 months of telmisartan and 36% with combination therapy. Both drugs, as well as their combination were also associated with a significant reduction in plasma BNP levels (9% with ramipril, 25% with telmisartan and 36% with combination treatment, $p < 0.001$) (Table 2).

Table 3 Characteristics of 40 patients with type 2 diabetes on the basis of echocardiographic left ventricular diastolic function at baseline

	Normal	Impaired relaxation	*p*-Value
N	15	25	_
Age (years)	51.3 ± 10	58.1 ± 7	0.027
Diabetes duration (years)	6.6 ± 4.7	9.5 ± 4.8	0.097
BMI (kg/m^2)	27.5 ± 3.2	28 ± 3	0.703
Waist to hip ratio	0.9 ± 0.004	0.9 ± 0.07	0.972
SBP (mmHg)	120 ± 9.5	125 ± 4.8	0.230
DBP (mmHg)	75 ± 5	76.1 ± 3.4	0.197
Fasting glucose (mmol/l)	146 ± 12	148.4 ± 8.6	0.114
HbA1c	6.3 ± 1.5	6.2 ± 1.6	0.213
Microalbuminuria	8.7 ± 4	12 ± 8	0.276
BNP (pg/ml)	15.8 ± 9.3	29.4 ± 18	0.038

Discussion

Many years have passed since the term *diabetic cardiomyopathy* was introduced to justify the symptoms of CHF in patients with diabetes, but no hypertension, left ventricular hypertrophy or CAD.[18] Diabetic cardiomyopathy can be manifested as diastolic and/or systolic dysfunction. In fact, it seems that altered diastolic function precedes the systolic damage and represents an early sign of DCM.[19,20]

Diastolic dysfunction and diabetes mellitus

Abnormal diastolic function is a common finding in both diabetic animals[1,2] and patients,[3–6] who lack any other predisposing factor for heart disease. In a recent study by Poirer et al.[21] LVDD was present in 28 (60%) of 46 men with type 2 diabetes, free of hypertension, CAD, CHF or diabetic complications. The prevalence of LVDD found in our study was concordant with that reported in these previous studies and was almost identical with that reported by Poirer et al., the only difference being the absence of subjects with pseudonormal pattern, probably due to the selection of patients at the earliest stages of DCM. Increased prevalence of LVDD has also been reported in patients with type 1 diabetes,[7] although that was not a universal finding in all studies.[22] Moreover, diastolic indices were more severely affected in type 2 than type 1 diabetic patients, both free of hypertension and CAD, in studies that involved mixed population,[23] which was attributed to the insulin resistance that characterizes the former population.

Pathogenesis of diabetic cardiomyopathy

The development of DCM is likely to be multifactorial[24,25] and RAS seems to play a pivotal role in this process.

Role of the renin–angiotensin system (RAS)

Diabetes is a condition of up-regulated RAS.[26] Angiotensin II, acting predominantly via type 1 receptors, cause a diverse range of adverse effects that ultimately promote the development of DCM; increased oxidative stress and inflammation, endothelial dysfunction, cardiomyocyte hypertrophy and apoptosis, myocardial fibrosis, vasoconstriction, thrombosis, plague rupture and the promotion of insulin resistance. Based on this

theoretical platform, the inhibition of RAS by an angiotensin converting enzyme inhibitor or/and an angiotensin II type 1 receptor blocker, could prevent or even reverse this situation.

BNP

BNP is a peptide hormone released primarily from the left ventricle in response to myocyte stretch due to volume expansion and pressure overload.[27] Plasma BNP levels in healthy subjects are extremely low in the venous blood, but rise under various pathologic conditions, such as CHF and asymptomatic systolic or diastolic LV dysfunction.[28] Patients with diabetes have higher plasma levels of BNP, compared with normal subjects, especially the subset of patients with microalbuminuria.[29] It has been proposed that BNP could serve as a potential marker of early heart failure as manifested by isolated diastolic dysfunction.[30] In another study, in patients with preserved LV systolic indices, BNP levels could reliably detect the presence of LV diastolic dysfunction, regardless of the presence of symptoms or not.[31] Patients in this study with a restrictive filling pattern had significantly higher BNP levels than patients with impaired relaxation, and patients with a pseudonormal pattern had intermediate values. Although a clear connection between plasma BNP levels and echocardiographic indices of LVDD in asymptomatic diabetic patients has not been established by other researchers,[32] in our study patients with abnormal LV relaxation had higher plasma BNP levels in comparison with patients with normal diastolic function (29.4 ± 18 vs 15.8 ± 9.3, $p = 0.038$). BNP by promoting vasodilation, diuresis and natriuresis improve hemodynamics in patients with isolated diastolic dysfunction and elevated BNP levels may actually represent a compensatory response of the heart.[33] Therefore, plasma BNP levels could not only serve as a screening tool for occult DCM, but also monitor appropriate therapeutic maneuvers, such as ACE-inhibitors and/or ARBs.

The effect of an ACE-inhibitor or an ARB on LV diastolic parameters and/or BNP has been mainly studied in hypertensive patients. In an elderly hypertensive population with LV hypertrophy temocapril (an ACE-inhibitor) was found to increase the transmitral E/A ratio and decrease plasma BNP levels.[34] Similarly, losartan (an ARB) normalized E/A ratio and other echocardiographic indices of LVDD in 728 patients with LV hypertrophy.[35] In another study which included 30 patients with essential hypertension, the combination of an ACE-inhibitor (namely perindopril) and an ARB (namely valsartan) produced a greater decline in plasma BNP levels than either drug alone, when used as monotherapy.[36] On the contrary, similar data in patients with type 2 diabetes are scarce and at least to our knowledge, our study is the first to compare the action and assess a possible salutary additive effect of an ACE-inhibitor and an ARB.

Study limitations

In this study we adopted many exclusion criteria in our attempt to focus on the primary stages of DCM. Therefore it was particularly difficult to recruit a large number of subjects. Consequently, the relative impact of various parameters, such as gender differences, was difficult to evaluate. In addition, ischemia was ruled-out by careful physical examination, detailed medical history and functional tests, such as dipyridamole-thallium scintigraphy or dobutamine stress echocardiography. Thus, although subtle atherosclerosis cannot be completely ruled-out, the total atherosclerotic burden should be very low to play any confounding role in the interpretation of the results. Transmitral and pulmonary venous flow recordings and not the relatively preload independent novel tissue Doppler imaging techniques were used as a marker of diastolic dysfunction.[37] The former methods, however, have proven to be reliable markers of LVDD and are widely used for this purpose in both the clinical practice and the research field.[21,31,38–40] BNP levels are within normal range at baseline and remain so throughout the study; however, the clear and significant tendency towards reduction of the BNP levels after all three therapeutic medications shown in our study cannot be ignored. Another issue is whether the beneficial effect of ramipril and telmisartan found in our study represent a class-effect (i.e. ACE-inhibitor and ARB, respectively); recent studies have shown that telmisartan due to its unique PPAR-γ activating action may exert extra anti-inflammatory, antioxidative, anti-proliferative and insulin-sensitizing properties.[41] A final limitation in our study is the lack of a placebo-controlled arm.

Conclusions

In conclusion, the following four are the major findings in our study: (a) the high prevalence of LVDD in otherwise healthy asymptomatic diabetic population without microalbuminuria, (b) the higher plasma BNP levels of patients with LVDD as compared to subjects with normal diastolic indices, (c) the favorable impact of ramipril, telmisartan and their combination on LV diastolic

indices and (d) the reduction of plasma BNP levels by all three therapeutic regimens.

Data about direct comparison between an ACE-inhibitor and an ARB, as well as a possible salutary additive action on echocardiographic and biochemical indices of diabetic cardiomyopathy have been scarce. Bearing in mind that our population consisted of otherwise healthy asymptomatic diabetic patients, free of microalbuminuria — and thus in the very early stages of diabetic complications — our findings enlighten the beneficial effect of RAS inhibition on the natural history of DCM and further emphasize the need for early intervention.

Hence, while it seems plausible that indeed early RAS inhibition might offer effective cardioprotection in diabetic patients and that plasma BNP levels could serve as reliable markers of therapeutic efficacy, larger clinical studies are warranted before wide application of our findings in clinical practice.

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