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Research Article

Early Initiation of Irbesartan Therapy Improves Cardiac and Kidney Function in Hypertensive Patients. Is This a Novel Pathway to Reduce HFpEF Incidence?

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Abstract

We evaluated the impact of irbesartan (150mg once/day for 6 months) on kidney function, echocardiographic parameters and pre-clinical atherosclerosis indexes in 33 patients with newly onset of hypertension and without overt kidney dysfunction (Hypertensive Group – HTG). 15 age- and sex-matched, normotensive, healthy individuals (normotensive group – NTG) served as controls, without receiving any medication. After 6 months, HTG further improved its kidney function, flow-mediated dilation, diastolic function, left ventricle mass and left atrium volume implicating a cardio and reno-protective action in patients with newly onset of hypertension.

Introduction

Angiotensin II Receptor Blockers (ARBs), are well-known anti-hypertensive medications with favourable effects on cardiac function and structure in hypertensive patients [1]. Meta-analyses support the reno-protective effects of ARBs, since they might maintain the residual kidney function in dialysis patients [2] or may slow down the progression of early kidney dysfunction to end-stage Chronic Kidney Disease (CKD) [3]. Current international guidelines have recommended the use of Angiotensin Converting Enzyme-inhibitors (ACEi) and alternatively ARBs, in preference to other anti hypertensive agents for treating hypertensive patients with mild CKD [4]. Notably, previous studies have examined the impact of ARBs on kidney function focusing hypertensive patients with established CKD of any degree.

The aim of the present study was to evaluate the impact of irbesartan, an ARB family member, on kidney function, echocardiographic parameters and pre-clinical atherosclerosis indexes in patients with newly onset of hypertension and without overt kidney dysfunction.

Methods

In our non-randomized study, we enrolled 33 patients (51.5% men), with newly onset hypertension (hypertensive group – HTG). Those patients had previously experienced side effects from ACEi and were the last month free from any chronic medication. A small group of 15 age- and sex-matched, normotensive, healthy individuals (Normotensive Group – NTG) served as controls. HTG received irbesartan 150mg once/day for 6 months and was evaluated at baseline and at the end. Evaluation included: Echocardiogram (cavities size and function, mitral inflow pattern, Left-Ventricle (LV) mass, Tissue Doppler Imaging - TDI), brachial artery Flow-Mediated Dilatation (FMD), Carotid artery Intima-Media Thickness (CIMT), and blood samples analysis (glucose, lipid, kidney profiles).

FMD Measurement

All tests were performed after overnight fasting. We inflated a blood pressure cuff, placed on the proximal forearm, 50mmHg above the systolic blood pressure for 5 minutes and we then

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deflated. We acquired and analyzed end-diastolic images of the brachial artery at baseline and 90 seconds after cuff deflation using the 7.5-mHz linear-array transducer (General Electric Logiq700, Riverside, USA). FMD was calculated by subtracting brachial artery average diameter at baseline from that at 90 seconds. Relative FMD was expressed as the percentage change from baseline (%FMD), divided by the baseline FMD.

Measurement of Carotid IMT

We performed a diagnostic high-resolution B-mode ultrasound of both carotids at baseline and at the end of the study. End-diastolic, B-mode images from longitudinal segments of each Common Carotid Artery (CCA), at 1-cm distance from the bifurcation on both walls, were allocated for CIMT measurement. We averaged CIMT measurements made over six cardiac cycles of each CCA and we then obtained the mean of left and right CCA IMT.

Statistical Analysis

Normally distributed continuous variables were expressed as the mean value ±SD and were compared within groups (paired-samples t-test) or between groups (student's t-test). Continuous variables with abnormal distribution presented as median with maximum and minimum values and Wilcoxon signed-rank test was used to assess within group differences. We considered a two-tailed $p<0.05$ as statistically significant. We used computer software package SPSS (version 23.0; SPSS Inc, Chicago, IL, USA) for statistical analysis.

Results

In HTG, the mean age was 61 years (33 years–78 years) and significant proportions had hyperlipidemia (42.4%), diabetes (15.2%) or obesity (21.2%) (BMI>30kg/m2), which did not alter significantly alter throughout the study. 6-month irbesartan treatment led to significant amelioration in both creatinine (p=0.008) and GFR (p=0.05) levels. With the exception of reduced cholesterol, the rest of biochemical parameters remained unaltered throughout the study.

Regarding echocardiographic parameters, irbesartan therapy significantly improved diastolic function as assessed by: deceleration time (p=0.001), tissue doppler imaging velocities (p=0.001), mitral E wave velocity (p=0.009). Besides this, there was a considerable reduction in LV mass (p=0.025), posterior wall thickness (p=0.043) and left atrial volume (p=0.02) within the irbesartan-treated group. That effect was associated with considerable increase in FMD after long-term irbesartan administration (p=0.006). In contrast, CIMT measurements did not change at all. All results are depicted in (Table 1a & b).

Discussion

In our drug-naïve, newly-onset, hypertensive population, 6-month irbesartan treatment exerted beneficial effects on kidney function, FMD, diastolic function, LV mass and left atrium volume.

It is well known that ARBs may prevent the onset of CKD or may slow down the progression of nephropathy in diabetic population, especially those with albuminuria [5]. In non-diabetic population, the reno-protective effects of ARBs are predominantly observed in hypertensive patients with moderate or advanced CKD [6], but it is still ambiguous in those with early (stage 1-3) CKD [7]. To our knowledge, this is the first report of increased GFR levels and lower creatinine levels in hypertensive patients with otherwise normal kidney function. That implicates a potential reno-protective effect of irbesartan, even when apparent kidney dysfunction is absent. This is of clinical importance, since the impairment of kidney function may mediate the development of heart failure with reduced ejection fraction (ischemic or non-ischemic). Recently, emerging data implicate that kidney dysfunction may also be involved in the pathogenetic process of heart failure with preserved ejection fraction [8]. Perhaps, ARBs may counter regulate HFpEF by improving kidney function, which remains to be proved. Besides this, our small study confirmed the previously mentioned favorable effects of ARBs on heart structure and diastolic function. Those effects are of clinical importance in the long-term. Taken together, a 6-month irbesartan therapy yielded dual cardiac and

Table 1a: Results of continuous variables with abnormal distribution at baseline and at the end of the study. Median values with (minimum and maximum values). Wilcoxon signed-rank test was used for comparison.

Variables	Baseline	End	p - value
IVS (mm)	9(7-13)	10(6-12)	0.162
PW (mm)	9(7-12)	9(6–12)	0.043
LV MASS	77.5(57.7-118)	75.5(55–157)	0.02
LAVI (ml/m^2)	29.8(16.1-56.4)	27(17–46)	0.025
EF (%)	60(52-70)	60(55–70)	0.409
DT (msec)	235(151-451)	212.5(155–303)	0.001
TDIS	13.75(10–21.6)	13.1(10–17.5)	0.272
TDISEP (cm/s)	7(4.5-13)	7.3(5.3–12.7)	0.01
SPV	0.625(0.5-0.8)	0.64(0.27–0.79)	0.896
Ht (%)	41.7(33.2-49)	41(35–52.6)	0.746
Hb (g/dl)	13.5(10.6-16.6)	13.3(11.6–17.7)	0.855
GLUCOSE (mg/dl)	95(62-207)	90(59–141)	0.061
CHOLESTEROL (mg/dl)	200(156-294)	191(154–260)	0.03
TRIGLYCERIDES (mg/dl)	110(40–180)	96(51–237)	0.145
URIC ACID (mg/dl)	5(3-7)	5.1(3–6.2)	0.423
GFR (ml/min/m^2)	78.64(47.55-213.31)	85.31(48.88–211.06)	0.05

IVS: Interventricular Septum; PW: Posterior Wall; LV: Left Ventricle; LAVI: Left-Atrium Volume Index; EF: Ejection Fraction; DT: Deceleration Time; TDISEP: Tissue Doppler Imaging Septum; FMD: Flow Mediated Dilatation

Table 1b: Results of continuous variables with normal distribution at baseline and at the end of the study.
Mean values with standard deviation values. Paired-samples t-test was used for comparison.

Variables	Baseline	End	p-value
EDD (mm)	46.8±3.84	46.76±3.3	0.909
RV diameter (mm)	34.84±3.61	35.02±3.2	0.693
RA area (cm^2)	15.91±1.83	15.95±1.56	0.913
MITRALE (m/s)	0.71±0.11	0.66±0.11	0.009
MITRALA (m/s)	0.82±0.16	0.81±0.15	0.702
TAPSE (mm)	23.5±3.3	22.88±17.93	0.261
TDIELAT (cm/s)	9.76±2.61	10.23±2.27	0.046
LCA IMT (mm)	7.66±1.61	7.62±1.6	0.73
RCA IMT (mm)	7.89±1.62	8.02±1.65	0.312
FMD (%)	5.98±3.74	7.48±3.92	0.006
UREA (mg/dl)	41.39±9.91	41.36±10.63	0.98
CREATININE (mg/dl)	1±0.27	0.95±0.26	0.008
Na (mmol/L)	140.41±2.53	140.84±2.55	0.377
K (mmol/L)	4.24±0.39	4.33±0.42	0.221

EDD: End-Diastolic Diameter; RV: Right Ventricle; RA: Right Atrium; mitrale: Mitral E Wave Velocity; mitrala: Mitral A Wave Velocity; TAPSE: Tricuspid Annular Plane Systolic Excursion; TDILAT: Tissue Doppler Imaging Lateral Wall; LCA IMT: Left Carotid Artery intima-Media Thickness; RCA IMT: Right Carotid Artery Intima-Media Thickness; FMD: Flow Mediated Dilatation

renal protective effects in our newly onset hypertensive population, without overt cardiac and kidney dysfunction.

Although this study was not powered to provide mechanistic explanation, we observed an association between kidney function improvement and FMD increase. FMD is positively correlated with the estimated glomerular filtration rate (eGFR), while it is considerably decreased in patients with CKD [9]. It has been hypothesized that ARBs may reduce Asymmetric Dimethylarginine (ADMA) production and oxidative stress and other hand may increase NO bioavailability, leading to NO-induced vasodilatation [10]. Such beneficial effects of ARBs on vascular resistance may explain the ARB-induced increase of FMD, which may increase kidney blood supply, ameliorating micro-vascular dysfunction and leading to improved kidney function.

Our main limitations are the small sample of HTG and the usage of simple kidney function parameters rather than more sophisticated and sensitive agents e.g. cystatin, which could have given us a better view of the kidney function and its changes.

In conclusion, our small study provides new evidence about the cardio and reno-protective effects of irbesartanin subjects with newly onset of hypertension and “normal” kidney function. The potential impact of our preliminary data to HFpEF requires further investigation.

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