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Olmesartan reverses not only vascular endothelial dysfunction but cardiac diastolic dysfunction in hypertensive patients with heart failure with preserved ejection fraction — ORION study

Eiichiro Yamamoto [a,*], Keisuke Ohba [a,b], Yoshihiro Hirata [a], Takanori Tokitsu [a], Koichiro Fujisue [a], Koichi Sugamura [a], Koichi Kaikita [a], Seiji Hokimoto [a], Seigo Sugiyama [a,c], Hisao Ogawa [a]

[a] Faculty of Life Sciences, Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan
[b] Cardiovascular Division, Yamaga Medical Center, Yamaga, Japan
[c] Cardiovascular Division Diabetes Care Center, Jinnouchi Hospital, Kumamoto, Japan

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The optimal treatment for heart failure (HF) with preserved left ventricular ejection fraction (LVEF) (HFpEF) has not been established [1], because the precise pathophysiological mechanism underlying HFpEF still remains unclear. Using experimental models of HFpEF, we previously reported a novel mechanism underlying reversal of endothelial dysfunction and HFpEF by antioxidant effects by AT_1-receptor blockade [2]. Furthermore, we recently demonstrated the clinical significance of derivatives of reactive oxidative metabolites (DROM, Diacron srl, Grosseto, Italy), a novel biomarker of reactive oxygen species (ROS), in HFpEF patients [3]. Hence, by performing this study (ORION: OlmesaRtan Improvement endothelial functiON with hypertension study), we examined the clinical therapeutic effect of AT_1-receptor blocker (ARB) on HFpEF patients.

We examined prospectively 20 hypertensive HFpEF patients, hospitalized in Kumamoto-University Hospital and taking any renin–angiotensin system (RAS) inhibitor other than highly-selective ARB; olmesartan for anti-hypertensive therapy, and switched to appreciable amounts of olmesartan. Olmesartan, a second generation ARB, has important interactions to evoke inverse agonism, so called "double-chain domain" [4], resulting in stronger angiotensin II blockade via high binding affinity to AT_1-receptor than angiotensin converting enzyme inhibitors (ACE-Is) and first generation ARBs. In the present study, hence, we used olmesartan among RAS inhibitors to elucidate the precise role of AT_1-receptor in HFpEF, and to examine the hypothesis that strong AT1-receptor blockade can clinically improve HFpEF through the inhibition of endothelial dysfunction. We defined HFpEF clinically according to the criteria of the European Working Group to HFpEF [5]. After the optimal therapy for HF, cardiac diastolic function estimated by echocardiography, peripheral vascular endothelial function assessed by fingertip-digital-reactive hyperemia-peripheral arterial tonometry (RH-PAT) using Endo-PAT2000, and blood various biomarkers at stable condition, and they were compared before (at the time of discharge) and 3-months after (at the visit in outpatient clinic) treatments of olmesartan. Non-invasive RH-PAT was performed with the patient in the supine position and both hands on the same level in a comfortable, thermoneutral environment.

11 of 20 HFpEF patients (55%) were taking ACEIs (enalapril 6, imidapril 5) and other 9 patients (45%) had the first generation ARBs (losartan 1, valsartan 5, candesartan 3). Other baseline characteristics of patients are shown in Table 1. Lipid profiles and renal functions in HFpEF patients were not changed by olmesartan treatments. Furthermore, the switch of antihypertensive drugs to olmesartan (average dosage amounts: 22.9 mg/day) didn't significantly affect systolic- and diastolic-blood pressure, heart rate, body mass index and abdominal circumference in HFpEF patients. Despite no additive hypotensive effects of olmesartan, endothelial dysfunction was significantly reversed (RH-index [RHI]; 1.57 ± 0.34 to 1.87 ± 0.50, $P = 0.034$), accompanied by significant reduction of serum DROM levels (normal range; 250–300 unit called the Carratelli unit [U.CARR]; 362.8 ± 13.7 to 302.1 ± 9.4 U.CARR, $P = 0.001$) (Table 1). Furthermore, olmesartan significantly improved cardiac diastolic dysfunction evaluated by the ratio of early-transmitral-flow velocity to tissue Doppler early-diastolic-mitral annular velocity (E/e′) (15.4 [11.0–21.4] to 11.0 [6.4–18.0], $P < 0.001$), but not LVEF and LV anterior wall thickness in echocardiography, and decreased plasma BNP levels (60.2 ± 75.1 to 22.7 ± 20.4 pg/mL, $P < 0.05$) in HFpEF patients (Table 1). Additionally, olmesartan significantly increased plasma superoxide dismutase (SOD) activity (2.39 ± 0.73 to 3.06 ±

* Corresponding author at: Department of Cardiovascular Medicine, Faculty of Life Sciences, Graduate School of Medical Science, Kumamoto University, 1-1-1 Honjo, Chuo-ku, Kumamoto 860-8556, Japan.
E-mail address: eyamamo@kumamoto-u.ac.jp (E. Yamamoto).

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Table 1
Changes in parameters of 20 HFpEF patients before and after the treatments of olmesartan.

	Before the treatments (n = 20)	After the treatments (n = 20)	P value[a]
Dosages of olmesartan	22.9 (7.2)	22.1 (8.5)	n.s.
Systolic blood pressure (mm Hg)	135.6 (17.7)	130.4 (20.7)	n.s.
Diastolic blood pressure (mm Hg)	76.9 (11.2)	75.0 (11.6)	n.s.
Heart rate (bpm)	70.3 (13.2)	66.1 (10.5)	n.s.
Body mass index	25.7 (3.1)	25.8 (2.7)	n.s.
abdominal circumference (cm)	91.1 (9.4)	91.4 (8.2)	n.s.
Hypertension (yes, %)	89.1	89.6	n.s.
LDL-Cho (mg/dL)	103.6 (38.5)	87.2 (29.9)	n.s.
HDL-Cho (mg/dL)	48.6 (8.6)	49.9 (11.2)	n.s.
Triglycerides (mg/dL)	130.3 (69.6)	112.7 (59.7)	n.s.
Glucose (mg/dl)	125.5 (51.3)	107.1 (20.4)	n.s.
Hb A1c (%)	6.42 (1.79)	6.01 (0.82)	n.s.
eGFR (mL/min/1.73 m^2)	72.6 (20.9)	67.3 (17.8)	n.s.
Creatinine (mg/dL)	0.80 (0.24)	0.76 (0.27)	n.s.
BUN (mg/dL)	16.4 (4.0)	15.8 (4.9)	n.s.
Na	140.2 (1.2)	140.2 (1.4)	n.s.
K	4.3 (0.4)	4.6 (0.4)	n.s.
RHI	1.57 (0.34)	1.87 (0.50)	0.034
LVEF (%)	63.5 (5.5)	63.3 (5.5)	n.s.
E/e′	15.4 (3.2)	11.0 (3.4)	<0.001
LVAW thickness (mm)	11.8 (3.0)	11.2 (2.5)	n.s.
Serum DROM levels (U.CARR)	362.8 (13.7)	302.1 (9.4)	0.001
Plasma BNP levels (pg/mL)	60.2 (75.1)	22.7 (20.4)	<0.05
Plasma SOD activity (U/mL)	2.39 (0.73)	3.06 (0.78)	0.02
Plasma adiponectin levels (μg/mL)	2.66 (1.55)	4.12 (1.99)	<0.05
Plasma NO_3^-/NO_2^- levels (μmol/L)	53.2 ± 28.1	62.9 ± 28.4	n.s.

Data are mean (standard deviation), median (25th to 75th percentile range), or number (percentage).
HF: heart failure, HFpEF: heart failure with preserved left ventricular ejection fraction, BMI: body mass index, CAD: coronary artery disease, DM: diabetes mellitus, Hb A1c: hemoglobin A1c, LDL-Cho: low-density lipoprotein cholesterol, HDL-Cho: high-density lipoprotein cholesterol, BNP: B-type natriuretic peptide, eGFR: estimated glomerular filtration rate, LVEF: left ventricular ejection fraction, E/e′: the ratio of early transmitral flow velocity to tissue Doppler early diastolic mitral annular velocity, LVAW: left ventricular anterior wall, ACEIs: angiotensin-converting enzyme inhibitors, ARBs: angiotensin II receptor blockers, CCB: calcium channel blockers, HMG-CoA RI: hydroxymethylglutaryl coenzyme A reductase inhibitors, BUN: blood urea nitrogen, Na: sodium, K: potassium, RHI: reactive hyperemia peripheral arterial tonometry index, DROM: derivatives of reactive oxygen metabolites, U.CARR: unit called the Carratelli unit, BNP: B-type natriuretic peptide, SOD: superoxide dismutase, NO_3^-/NO_2^-: nitrates-and-nitrite.
[a] Comparison between before and after the treatments of olmesartan for HFpEF patients.

0.78 U/mL, P = 0.02) and adiponectin levels (2.66 ± 1.55 to 4.12 ± 1.99 μg/mL, P < 0.05) but not affect plasma nitrates and nitrites (NO_3^-/NO_2^-) levels (53.2 ± 28.1 to 62.9 ± 28.4 μmol/L) (Table 1). Thus, strong AT_1-receptor blockade by olmesartan restored not only endothelial dysfunction but also cardiac diastolic dysfunction in HFpEF patients beyond hypotensive effects.

Several studies reported that ROS were closely associated with the pathophysiology of endothelial dysfunction in various cardiovascular diseases [6], and we reported that peripheral vascular endothelial function, assessed by RH-PAT, is significantly impaired [7] and ROS, indicated by increased serum DROM values, were significantly overproduced in HFpEF patients than in non-HF patients [3]. In this study, actually, both peripheral endothelial dysfunction and ROS overproduction significantly occurred in HFpEF patients. Furthermore, strong AT_1-receptor blockade by olmesartan significantly decreased ROS and improved endothelial dysfunction in HFpEF, consistent with our basic research using HFpEF model rats [2]. Moreover, our previous basic research demonstrated that AT_1-receptor blockade also reversed cardiac diastolic dysfunction and inhibited cardiac death of HFpEF rats [2]. Likewise, the present clinical study showed that olmesartan significantly improved HF, indicating that AT_1-receptor is deeply involved in the pathophysiology of HFpEF.

As described above, the precise pathophysiological mechanism underlying HFpEF remains unknown. Although ROS might be one of the major risk factors for the development of HFpEF [8], the mechanisms of ROS overproduction in HFpEF are not fully understood. In this study, olmesartan significantly increased SOD activities, but not nitric oxide (NO) levels, indicating that angiotensin receptor-induced SOD inactivation might involve in ROS overproduction in HFpEF. Actually, previous reports showed that angiotensin II-decreased SOD activation in cardiovascular diseases [9]. Adiponectin, one of the anti-atherogenic adipokines, was reported to be downregulated by angiotensin II-induced ROS [10]. Therefore, some ARBs were reported to inhibit ROS and upregulate adiponectin, leading to the improvement of endothelial dysfunction as well as the beneficial effects of olmesartan demonstrated in this study. Thus, we confirmed that increased SOD, but not NO activities, might contribute to beneficial effects of ARB for endothelial function and cardiac diastolic function in HFpEF. However, further investigations are needed to elucidate detailed mechanisms and involvements of ROS in HFpEF.

HFpEF patients have a poor prognosis equivalent to that with HF with reduced LVEF patients. Therefore, identification of effective therapeutic strategy for HFpEF has great clinical importance. No clinical study demonstrated the efficacy of RAS inhibitors for the management of HFpEF, however this study showed that olmesartan clinically improved endothelial dysfunction and cardiac diastolic dysfunction, both of which are known to be associated with adverse clinical outcome of HFpEF. These results indicate that olmesartan could contribute to the improvement of prognosis in HFpEF.

Drug-induced changes in endothelial function should be performed ideally in a cross-over matter, in particular with such small-sample-sized study. Cross-over or further large studies are required to determine the exact significance of olmesartan in HFpEF patients. Despite the limitation, this study clearly showed the beneficial effects of highly-selective AT_1-receptor blockade by olmesartan in HFpEF, indicating the useful therapeutic strategy of strong AT_1-receptor blockade for HFpEF.

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Conflict of interest disclosures

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