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Original Article

Curative effect analysis of urapidil on heart failure with preserved ejection fraction and heart failure with reduced ejection fraction

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Abstract: The aim of this study was to evaluate whether urapidil, an a1-adrenoceptor antagonist and 5-HT1A receptor agonist, could provide additional therapeutic benefits compared with nitroglycerin (NG) in acute heart failure with preserved ejection fraction (HFpEF) or acute heart failure with reduced ejection fraction (HFrEF) concomitant by hypertension. This study enrolled a total of 194 patients who had been diagnosed with acute HFpEF or acute HFrEF from multiple medical centers between August 2011 and November 2013. Urapidil (100 mg/day) and NG (10 mg/day) were diluted in 50 mL of 0.9% normal saline and intravenously delivered to patients within periods of 48 to 140 hours. Related clinical indexes were routinely monitored and analyzed with specific statistical procedure. In both acute HFpEF group and acute HFrEF group, compared with NG, urapidil has a remarkable time-dependent reducing effect on multiple clinical indexes, including SBP, DBP, HR and NT-proBNP (72-hour and 7-day). Compared with HFrEF group, HFpEF group had lower levels of SBP, NT-proBNP (72-hour and 7-day) and LA response to urapidil treatment, and LVEF level in HFpEF group was improved significantly after 7-day urapidil treatment, suggesting that urapidil treatment make HFpEF patients benefit more. There was no significant difference of blood pressure between two groups after urapidil treatment. For acute HFpEF and HFrEF patients with hypertension, intravenous administration of urapidil is a promising treatment for the better control of blood pressure and preserved cardiac function. Urapidil treatment should be recommended for HFpEF.

Keywords: Urapidil, heart failure, HFpEF, HFrEF

Introduction

As a common clinical syndrome with high morbidity and mortality, heart failure (HF) is a major worldwide public health problem [1]. HF is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) and accompanied signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral edema), which are caused by a structural and/or functional cardiac abnormality. Clinical trials showed that HF resulted in a reduced cardiac output and/or elevated intracardiac pressures at resting or stressed state. HF patients often have lower EF. However, recent researches indicated that more than 50% of HF patients with the clinical syndrome have normal left ventricular ejection fractions [2, 3]. Compared with classic "heart failure with reduced ejection fraction" (HFrEF), these cases can therefore be termed "heart failure with preserved ejection fraction" (HFpEF) [2, 3].

HFpEF and HFrEF have different pathophysiologic mechanisms and comorbidities, so the clinical treatments should be differentiated. However, considering the efficacy to improve the disturbed hemodynamics, vasodilators were recognized as the 1st-line treatment options currently during the acute period for both kinds of these HF diseases [4].

Among the vasodilators, nitroglycerin (NG) has been widely used to treat acute HF [5]. The main effect of NG is to dilate the vein so as to alleviate preload of the heart by decreasing returned blood volume. Moreover, low doses of NG cannot induce a promising effect on the periphery arteriole. Thus, NG would not reduce

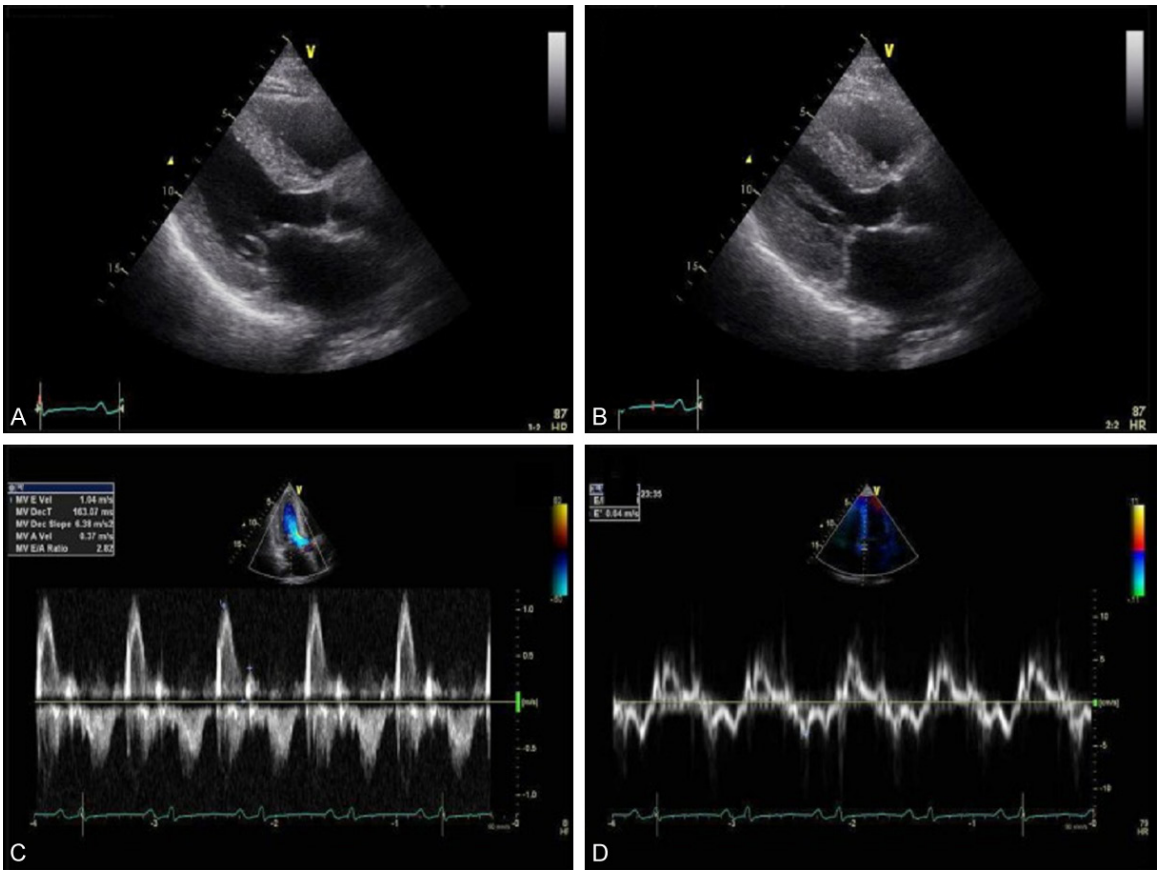

Figure 1. Echocardiography features of HFpEF patients (ie, HR=60 beats/min, E/A=95/65, IVRT=48 ms), the isovolumic relaxation time was shortened.

peripheral vascular resistance, alleviate afterload of the heart or increase the left cardiac output quickly [6, 7]. However, high doses of NG may cause hypotension and reflex tachycardia, which may further deteriorate cardiac function [8].

Urapidil is currently used to treat both acute hypertensive crisis and acute HF [9, 10]. Urapidil is a peripheral postsynaptic alpha-adrenergic antagonist with additional central stimulating effects at 5-HT1A receptors. It can induce rapid central and peripheral vasodilation effects. Unlike other α1-adrenoceptor antagonists, urapidil does not cause tachycardia or drug induced hypotension [11]. Several clinical trials have shown that urapidil can improve cardiac function and effectively reduce heart rate (HR) in HF patients [12, 13].

Despite the above-mentioned clinical evidences, the overall data is inconclusive on the application of urapidil in HFpEF and HFrEF patients. Therefore, the major purpose of this study was to identify the safety and efficacy of urapidil and explore whether urapidil exerts extra beneficial effects on concurrent disorders in HFpEF and HFrEF patients. A multicenter, randomized, parallel control trial was performed to evaluate the efficacies of urapidil and NG on the treatment of acute HFpEF and HFrEF patients in China.

Methods

Patients

From August 2011 to November 2013, this study enrolled a total of 194 patients who had been diagnosed with acute HFpEF or acute HFrEF concurrent with hypertension and were admitted to the following medical centers across China: Emergency Department and cardiology Department of Xuan Wu Hospital Capital Medical University, Beijing Friendship Hospital, Beijing An Zhen Hospital, Beijing Tong Ren Hospital, Affiliated Hospital of Chongqing Medical University, Zhejiang Sir Run Shaw

Table 1. Analysis for SBP and DBP in HFrEF groups under Urapidil or NG treatment

		SBP (0 hour)	SBP (24-hour)	SBP (48-hour)	SBP (72-hour)	SBP (7-day)
Urapidil	Mean (mmHg)	160.90	145.68	133.97	126.90	121.10
	N	31	31	31	31	31
	Std. Deviation	17.034	18.128	16.130	13.375	10.264
NG	Mean (mmHg)	161.64	148.40	140.71	135.14	128.29
	N	42	42	42	42	42
	Std. Deviation	16.282	21.272	15.728	16.047	14.336
		DBP (0 hour)	DBP (24-hour)	DBP (48-hour)	DBP (72-hour)	DBP (7-day)
Urapidil	Mean (mmHg)	83.74	74.39	71.87	69.87	67.87
	N	31	31	31	31	31
	Std. Deviation	20.285	14.068	10.459	7.018	6.980
NG	Mean (mmHg)	83.74	75.10	71.81	69.45	70.10
	N	42	42	42	42	42
	Std. Deviation	18.812	16.610	10.778	6.894	7.821

Hospital, Affiliated Hospital of Tongji University, Shandong Qilu Hospital, First Hospital Affiliated with Jilin University, First Hospital Affiliated with Haerbin Medical University and Guangdong General Hospital. All the enrolled patients belonged to the New York Heart Association (NYHA) II-IV. Acute HFpEF and acute HFrEF were confirmed for all enrolled patients according to ESC guidelines [1]. Urapidil and nitroglycerin (NG) were administered for both groups, respectively. NG was used in this study to represent the traditional vasodilator.

Each patient provided a signed informed consent prior to enrollment in the study. All clinical procedures were performed in accordance with guidelines established by the Declaration of Helsinki, and the study protocol was approved by the Clinical and Animal Research Ethics Committees of Capital Medical University, China.

Inclusion criteria and exclusion criteria

Echocardiography features of HFpEF patients were shown in **Figure 1**. Inclusion criteria for enrolled patients were as follows: 1) Meet the standard diagnostic criteria for hypertension: systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure (DBP) of >90 mmHg, or regularly taking anti-hypertensives in accordance with the 2010 Chinese guidelines for the management of hypertension [14]. 2) Meet the standard diagnostic criteria for HFpEF: LVEF measured by echocardiography on admission ≥45%. 3) Meet the standard diagnostic criteria for HFrEF: LVEF measured by echocardiography on admission <45%.

Exclusion criteria were as follows: Systolic blood pressure (SBP) <100 mmHg; severe valve stenosis; acute coronary syndrome; restrictive cardiomyopathy or constrictive pericarditis; obstructive hypertrophic cardiomyopathy; evidence of cardiogenic shock or other cardiovascular disorder contradicting intravenous administration of a vasodilator; acute phase of some other pulmonary disease; severe chronic obstructive pulmonary disease; severe liver diseases (>3-fold maximum normal values of alanine aminotransferase and aspartate transaminase); kidney (>2-fold maximum normal value of creatinine) insufficiency; malignant or psychiatric disease or currently taking other medications or being enrolled in another clinical trial; history of allergy to NG or urapidil.

Medications prior to admission

Among the 194 enrolled patients, 183 were taking antihypertensive medications, including calcium channel blocker, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, diuretics and β-blockers.

Drug delivery

Doses of urapidil and NG were administered to patients based on the standard protocols used for regular administration regimes for acute HF patients. Urapidil (100 mg; BykGulden, Leverkusen, Germany) and NG (10 mg; Beijing Yimin, Beijing, China) were diluted in 50 mL of 0.9% normal saline and intravenously delivered to patients within periods of 48 to 140 hours. Urapidil was administered at a rate of 50 or 100 mg/min for an initial 6 hours and then

Table 2. Analysis for SBP and DBP in HFpEF groups under Urapidil or NG treatment

		SBP (0 hour)	SBP (24-hour)	SBP (48-hour)	SBP (72-hour)	SBP (7-day)
	Mean (mmHg)	167.77	143.94	135.01	126.43	119.06
Urapidil	N	88	88	88	88	88
	Std. Deviation	18.121	19.223	19.345	12.975	19.162
	Mean (mmHg)	166.00	143.03	138.02	133.11	128.86
NG	N	64	64	64	64	64
	Std. Deviation	17.323	18.987	17.324	13.045	17.345
		DBP (0 hour)	DBP (24-hour)	DBP (48-hour)	DBP (72-hour)	DBP (7-day)
	Mean (mmHg)	87.04	77.12	70.13	68.07	67.03
Urapidil	N	88	88	88	88	88
	Std. Deviation	10.345	15.213	8.421	9.322	7.232
	Mean (mmHg)	88.13	76.97	74.39	71.35	69.34
NG	N	64	64	64	64	64
	Std. Deviation	9.098	11.421	9.321	7.821	7.009

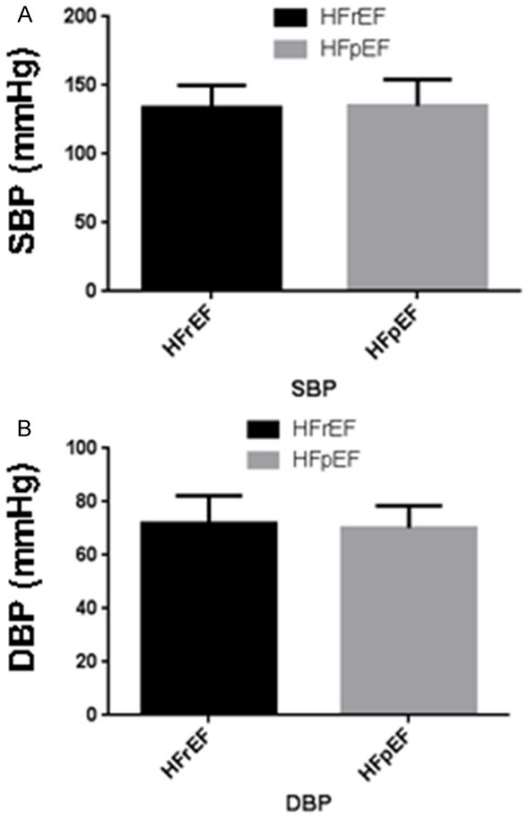

Figure 2. Measurement of blood pression. A. Analysis of average SBP for HFrEF and HFpEF patients under Urapidil treatment; B. Analysis of average DBP for HFrEF and HFpEF patients under Urapidil treatment.

adjusted to 300 mg/min for the remaining administration time. Accordingly, NG was administered at a rate of 10 mg/min for the initial 6 hours and then adjusted to a maximum rate of 20 mg/min for the remaining administration time.

The blood pressure (BP) was constantly monitored during administration to provide constant information that might warrant adjustment of the dose rate and delivery time.

Parameters for clinical assessment

During the treatment with either NG or urapidil, the following clinical indexes were routinely monitored: HR, SBP, diastolic blood pressure (DBP), NT-proBNP levels (admission, 24 hours, 48 hours, 72 hours and 7 days after treatment), red blood cell distribution width, liver function (total bilirubin, ALT and AST), kidney function (creatinine, blood urea nitrogen), lipid profiles (triglyceride, total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol), fasting and postprandial plasma glucose (FPG and PPG), glycohemoglobin and echocardiogram results (left atrium, left ventricular ejection fraction [LVEF], left ventricular cardiac output, early diastolic filling to atrial filling velocity ratio of mitral flow, left ventricular end diastolic volume, CI). For all echocardiography studies, double-blind study was used for the performers and patients during the operation and data collection.

Statistical analysis

All data were analyzed using SPSS for Windows, Version 22.0 (SPSS Inc, Chicago, IL). Values for continuous variables are displayed as the Mean ± Standard Deviation. Multivariate analysis of variance was performed to analyze repeated-measures data. *P*-values <0.05 and <0.01 were considered as statistically significant difference and highly significant difference, respectively.

Table 3. Analysis for heart rates in HFrEF groups under Urapidil or NG treatment

		HR (0 hour)	HR (24-hour)	HR (48-hour)	HR (72-hour)	HR (7-day)
Urapidil	Mean (per minutes)	91.35	83.68	80.48	76.06	73.03
	N	31	31	31	31	31
	Std. Deviation	18.198	16.177	14.047	10.122	8.616
NG	Mean (per minutes)	91.38	84.98	82.93	79.71	75.52
	N	42	42	42	42	42
	Std. Deviation	22.874	14.314	12.748	9.366	8.329

Table 4. Analysis for heart rates in HFpEF groups under Urapidil or NG treatment

		HR (0 hour)	HR (24-hour)	HR (48-hour)	HR (72-hour)	HR (7-day)
Urapidil	Mean (per minutes)	85.56	76.06	73.91	71.72	70.99
	N	88	88	88	88	88
	Std. Deviation	15.340	12.240	11.897	10.475	7.696
NG	Mean (per minutes)	84.06	77.45	75.48	74.02	71.46
	N	64	64	64	64	64
	Std. Deviation	15.267	12.240	12.064	8.881	7.324

Table 5. Analysis for NT-proBNP in HFrEF groups under Urapidil or NG treatment

		NT-proBNP (0 hour)	NT-proBNP (24-hour)	NT-proBNP (48-hour)	NT-proBNP (72-hour)	NT-proBNP (7-day)
Urapidil	Mean (ng/ml)	6549.032	4772.6452	3592.2952	2526.442	1580.9355
	N	31	31	31	31	31
	Std. Deviation	5193.3798	3927.05403	3032.17704	2011.9981	1182.50116
NG	Mean (ng/ml)	5693.948	4883.1476	4154.3095	3331.643	3025.5690
	N	42	42	42	42	42
	Std. Deviation	5328.9479	4776.22947	3907.95386	3212.8198	2710.48462

Table 6. Analysis for NT-proBNP in HFpEF groups under Urapidil or NG treatment

		NT-proBNP (0 hour)	NT-proBNP (24-hour)	NT-proBNP (48-hour)	NT-proBNP (72-hour)	NT-proBNP (7-day)
Urapidil	Mean z (ng/ml)	3931.722	3330.1875	2483.872	1675.784	944.049
	N	88	88	88	88	88
	Std. Deviation	3361.8982	2559.70802	2291.5359	1387.8637	556.7254
NG	Mean (ng/ml)	5423.905	3853.2966	2878.708	2516.844	2201.798
	N	64	64	64	64	64
	Std. Deviation	5182.2844	3779.0242	2660.8111	1643.3513	1442.7710

Results

Urapidil treatment reduced blood pressure of heart failure patients

Compared with NG treatment, urapidil treatment significantly reduced levels of SBP and DBP of heart failure patients (**Tables 1** and **2**; **Figure 2**, $P<0.05$), which was observed in both acute HFrEF group and acute HFpEF group, suggesting urapidil treatment has a promising effect on blood pressure control. Urapidil treatment indeed controlled blood pressure in both acute HFrEF group and acute HFpEF group, while there was no significant difference of blood pressure in two groups after urapidil treatment.

Urapidil treatment control heart rates

Compared with NG treatment, patients under urapidil treatment had a significantly lower lev-

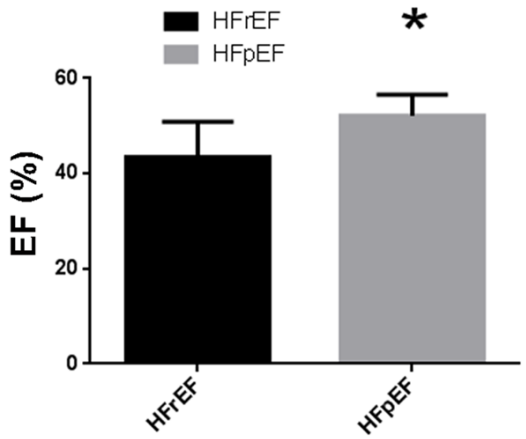

Figure 3. Analysis of 7-day LVEF for HFrEF and HFpEF patients under Urapidil treatment, P<0.0001.

els of HR (**Tables 3** and **4**, *P*<0.05), and this effect was also observed in both acute HFpEF group and acute HFrEF group, suggesting urapidil treatment controlled heart rates.

Urapidil treatment decreased level of NT-proBNP at different time points

Compared with NG treatment, patients under urapidil treatment had a significantly decreased levels of NT-proBNP (**Tables 5** and **6**, *P*<0.05), and this effect was observed in both acute HFpEF group and acute HFrEF group, suggesting Urapidil treatment decreased level of NT-proBNP. Moreover, two NT-proBNP tests at different time points (72-hour and 7-day) showed the same therapeutic effect, which indicated that urapidil was superior to NG treatment.

Urapidil treatment improved cardiac function of HFpEF patients

Compared with acute HFrEF group, acute HFpEF group had a higher improvement of LVEF after 7-day urapidil treatment (**Figure 3**, *P*< 0.05), suggesting urapidil treatment improved cardiac function of HFpEF patients.

Urapidil treatment had evident effects on multiple test indexes in HFpEF patients

Compared with acute HFrEF group, urapidil treatment had evident effects on multiple test indexes in acute HFpEF group, including lower levels of SBP, decreased concentration of NT-proBNP (72-hour and 7-day) and reduced LA (**Figure 4**, *P*<0.05).

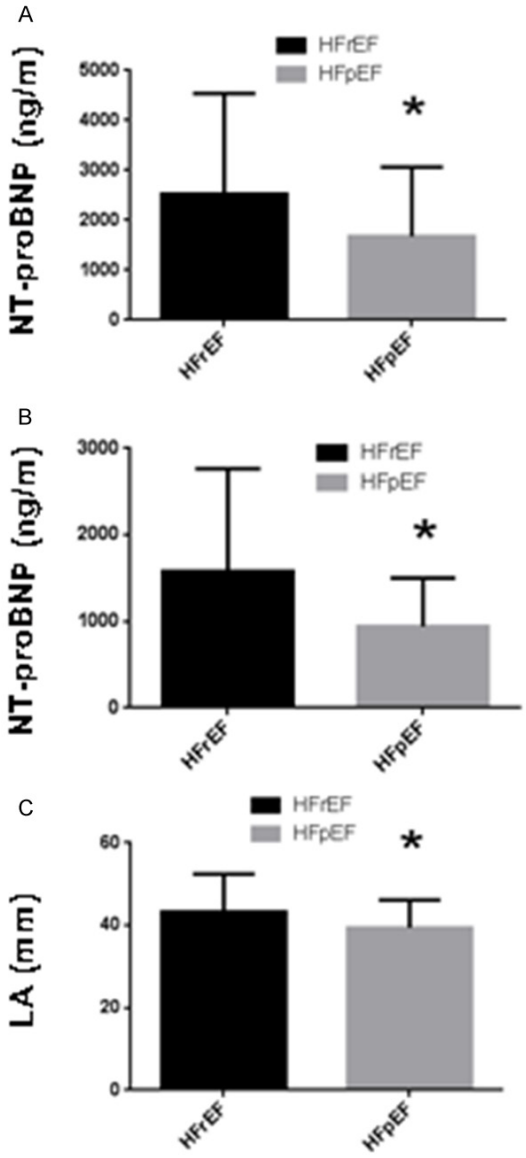

Figure 4. Heart failure indices measurement. A. Analysis of 72-hour NT-proBNP for HFrEF and HFpEF patients under Urapidil treatment; B. Analysis of 7-day NT-proBNP for HFrEF and HFpEF patients under Urapidil treatment; C. Analysis of average LA diameter for HFrEF and HFpEF patients under Urapidil treatment.

Urapidil lowered both the level of glucose and the level of lipid

Compared with NG treatment, urapidil treatment significantly reduced levels of glucose and improved the lipid profile in heart failure patients, and this effect was observed in both acute HFrEF group and acute HFpEF group (**Table 7**, P<0.001), suggesting Urapidil treatment has a promising effect on control of metabolism.

Table 7. Analysis for glucose and the lipid in HFrEF group and HFpEF group under urapidil or NG treatment

	HFrEF				HFrEF			
	Urapidil (N=31)		NG (N=42)		Urapidil (N=88)		NG (N=64)	
	Mean (mmol/L)	SD	Mean (mmol/L)	SD	Mean (mmol/L)	SD	Mean (mmol/L)	SD
GLU (0 hour)	9.29	2.76	11.31	2.71	10.04	1.57	11.09	2.46
GLU (24-hour)	10.77	1.68	12.39	2.32	9.24	1.15	11.13	2.19
GLU (48-hour)	8.55	2.56	10.77	2.67	8.18	2.19	9.81	2.35
GLU (72-hour)	7.02	3.12	7.17	3.74	6.37	2.40	7.03	1.75
GLU (7-day)	5.71	1.67	6.12	1.73	5.45	1.37	6.44	1.41
LDL (0 hour)	2.37	1.16	2.41	0.79	2.31	1.09	2.44	0.83
LDL (48-hour)	2.21	0.86	2.38	0.84	2.20	0.84	2.40	0.85
LDL (7-day)	2.16	0.87	2.38	0.83	2.05	0.83	2.23	0.84
HDL (0 hour)	1.13	0.39	1.18	0.22	1.23	0.34	1.20	0.32
HDL (48-hour)	1.29	0.51	1.21	0.45	1.35	0.63	1.24	0.51
HDL (7-day)	1.31	0.45	1.25	0.30	1.42	0.33	1.31	0.40

Discussion

Globally, HF has been recognized as one of the major cardiovascular disorder with high morbidity/mortality and heavy social burden. Previous studies indicated that HF even had a worse five-year prognosis than cancer [15, 16]. Nowadays, increasing studies show that despite many patients with a clinical diagnosis of HF have lower EF, approximately 50% of patients have a normal or near normal ejection fraction (EF) [2, 17, 18]. Accordingly, HF has been classified into HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF) according to LVEF [16].

The two types of HF treatment should be differentiated due to the difference in pathogenesis. Studies had showed that patients with HFpEF had higher systolic blood pressure compared with patients with HFrEF [17, 18]. In addition, ischemic heart disease is the main cause of HFrEF, while myocardial infarction and angina were significantly less common in HFpEF compared with HFrEF. Thus, patients with HFpEF were less likely to be prescribed HF medications (e.g. ACE inhibitors/ARBs, beta-blockers, and aldosterone antagonists) than those with HFrEF. Although all patients with either acute or chronic heart failure have impaired cardiac function, those with AHF are characterized by elevated filling pressures, high systemic vascular resistance, and hypertension. These features not only lead to “pump failure”, but also further reduce perfusion to vital organs to cause vascular failure [19, 20]. ESC guidelines indicate that, for these two types of HF, vasodilators should be used when the acute HF occurs [18, 19]. Among vasodilators, NG is traditionally used to alleviate HF symptoms.

This is a multicenter, randomized, parallel-control trial conducted in China. Efficacies were compared between urapidil and NG in the treatment of HFpEF and HFrEF patients with hypertension. Here hypertension was selected as a complicate factor because it represents the most common concurrent disease in HF patients. As expected, both drugs effectively reduced the SBP and DBP in both HFpEF patients and HFrEF patients. But urapidil can reduce the blood pressure more effectively. Urapidil not only can affect peripheral postsynaptic alpha-adrenergic antagonist, but also has additional central stimulating effects at 5-HT1A receptors. Therefore, it can produce rapid central and peripheral vasodilation effects. Urapidil showed better efficacy on SBP control than NG. Hypertension may have a stronger negative impact on HFpEF due to ventricular-vascular coupling for it is a key factor for the development of left ventricular hypertrophy and diastolic dysfunction [21, 22]. Accordingly, the lower blood pressure may delay left ventricular remodeling and bring more benefit to the HFpEF patients. Moreover, our study showed that compared with NG treatment, the LA was significantly decreased after urapidil treatment.

Our study indicated that urapidil reduced and stabilized the HR of both HF subtypes. Unlike some other α1-adrenoceptor antagonists, ura-

pidil does not elicit reflex tachycardia. Urapidil's primary effect is as an alpha-blocker. But it also has another effect-central sympatholytic effect mediated via stimulation of serotonin 5HT1A receptors in the central nervous system [23]. The 5HT1A agonist effects of urapidil decrease the firing rate of serotonergic neurons, which inhibits their excitatory input to sympathetic neurons. This inhibition depresses sympathetic nervous system activity at the receptor level. In addition to the contribution to the reducing of peripheral resistance, this reduced sympathetic tone appears to suppress the reflex tachycardia, which is always associated with vasodilator therapy. NT-proBNP exists in the ventricular muscle mainly and the quality of its production changes with the filling pressure. Previous studies have reported that NT-proBNP could be regarded as a marker for diagnosis or exclusion of HF. Hypertension can lead to pressure overload, which further impairs cardiac function. Urapidil is proven to exert its antihypertensive action via both peripheral alpha-adrenergic receptor and central HTR1A antagonizing effects, which makes it more effective for the regulation of afterload [24]. Urapidil can reduce cardiac afterload via decreasing NT-proBNP, and finally improve cardiac function. Previous studies have also indicated that serum NT-proBNP is of significant prognostic value in patients with HFpEF, and the rise in NT-proBNP is associated with an increasing risk of adverse cardiovascular outcome (a fall was associated with a decrease in risk) [25, 26]. Our post-hoc analysis in patients with HFpEF indicated that urapidil may have an immediate inhibitory effect on serum NT-proBNP within 7 days of treatment. From this perspective, the present pilot study suggests that urapidil may be beneficial for AHF patients with HFpEF.

Urapidil may have a beneficial effect on both glucose and lipid metabolism [24]. In HFpEF group and HFrEF group, urapidil can lower both the level of glucose and the level of lipid. Intravenous urapidil showed no association with any impairment in renal or hepatic function, and patients experienced fewer of the adverse events, including headache and tachycardia. These findings indicated that urapidil had more remarkable efficacy in blood pressure and cardiac protective functions. Biochemical indices reflecting hepatic and renal function were not significantly changed after urapidil administration and there was no significant difference between urapidil group and NG group, which confirmed urapidil's safety in HF treatment.

Like other α-blockers, urapidil also has side effects, such as dizziness, nausea and vomiting, which were induced by a rapid reduction in BP [27]. But, as urapidil is lack of central effects on 5-HT receptors, those side effects were minimized. The results of this study implied that both HFpEF patients and HFrEF patients can tolerate the moderate side effects of urapidil. Moreover, urapidil showed some additional advantages over traditional antihypertensive medications. For example, urapidil may decrease blood pressure smoothly, and it does not influence the metabolic profile. Based on our study, the results implied that although both NG and urapidil showed significant therapeutic effects on HFpEF patients and HFrEF patients with hypertension, urapidil seemed to be a better option for these patients and led better long-term clinical outcomes. Current vasodilators are often poorly tolerated by many AHF patients for adverse events [28, 29]. Accordingly, we proved that acute heart failure (include HFpEF and HFrEF) patients with hypertension were less troubled by headache and tachycardia with administration of urapidil.

There were also some limitations in this study. This study was not designed with adequate power to evaluate the potential benefits of urapidil in patients with HFpEF. The observation period is relative short, and the study design has restricted the ability to properly assess the long-term clinical outcome for patients receiving urapidil. The re-hospitalization rate or mortality was not evaluated in this study, whether urapidil can improve rates of re-hospitalization or mortality at the one-month follow-up was still unknown. Further study with larger sample size and better design is needed.

In conclusion, our study indicates that, for acute HFpEF and HFrEF patients with hypertension, the treatment effect of intravenous administration of urapidil on blood pressure and preserved cardiac function was better compared with intravenous of nitroglycerin, moreover, it has less adverse side effects. Urapidil may be a promising candidate for the treatment of acute heart failure (include HFpEF and HFrEF).

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Written informed consent was obtained.

Disclosure of conflict of interest

None.

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References

[1] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; ESC Scientific Document Group. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European society of cardiology (ESC) developed with the special contribution of the heart failure association (HFA) of the ESC. Eur Heart J 2016; 37: 2129-2200.

[2] Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL and Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006; 355: 251-259.

[3] Lee DS, Gona P, Vasan RS, Larson MG, Benjamin EJ, Wang TJ, Tu JV and Levy D. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the framingham heart study of the national heart, lung, and blood institute. Circulation 2009; 119: 3070-3077.

[4] Wakai A, McCabe A, Kidney R, Brooks SC, Seupaul RA, Diercks DB, Salter N, Fermann GJ and Pospisil C. Nitrates for acute heart failure syndromes. Cochrane Database Syst Rev 2013; CD005151.

[5] Carlson MD and Eckman PM. Review of vasodilators in acute decompensated heart failure: the old and the new. J Card Fail 2013; 19: 478-493.

[6] Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW and Yancy CW. 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: a report of the american college of cardiology foundation/American heart association task force on practice guidelines: developed in collaboration with the international society for heart and lung transplantation. Circulation 2009; 119: 1977-2016.

[7] Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG and Swedberg K. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European society of cardiology. Developed in collaboration with the heart failure association of the ESC (HFA) and endorsed by the European society of intensive care medicine (ESICM). Eur Heart J 2008; 29: 2388-2442.

[8] Ramey JT and Lockey RF. Allergic and nonallergic reactions to nitroglycerin. Allergy Asthma Proc 2006; 27: 273-280.

[9] Holzer-Richling N, Holzer M, Herkner H, Riedmuller E, Havel C, Kaff A, Malzer R and Schreiber W. Randomized placebo controlled trial of furosemide on subjective perception of dyspnoea in patients with pulmonary oedema because of hypertensive crisis. Eur J Clin Invest 2011; 41: 627-634.

[10] Stangl K, Dschietzig T, Richter C, Laule M, Stangl V, Tanis E, Baumann G and Felix SB. Pulmonary release and coronary and peripheral consumption of big endothelin and endothelin-1 in severe heart failure: acute effects of vasodilator therapy. Circulation 2000; 102: 1132-1138.

[11] Verberne AJ and Rand MJ. Effect of urapidil on beta-adrenoceptors of rat atria. Eur J Pharmacol 1985; 108: 193-196.

[12] Minushkina LO. Features of urapidil in treatment of resistant hypertension. Kardiologiia 2012; 52: 77-82.

[13] Vanhaesebrouck S, Hanssens M and Allegaert K. Neonatal transient respiratory depression after maternal urapidil infusion for hypertension. Eur J Pediatr 2009; 168: 221-223.

[14] Alijotas-Reig J, Bove-Farre I, de Cabo-Frances F and Angles-Coll R. Effectiveness and safety of prehospital urapidil for hypertensive emergencies. Am J Emerg Med 2001; 19: 130-133.

[15] Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Swei-

tzer NK, Yang S and McKinlay SM. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014; 370: 1383-1392.
[16] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ and Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American college of cardiology foundation/American heart association task force on practice guidelines. Circulation 2013; 128: e240-327.
[17] Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y and Liu PP. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006; 355: 260-269.
[18] Bursi F, Weston SA, Redfield MM, Jacobsen SJ, Pakhomov S, Nkomo VT, Meverden RA and Roger VL. Systolic and diastolic heart failure in the community. JAMA 2006; 296: 2209-2216.
[19] Adams KF Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, Berkowitz RL, Galvao M and Horton DP. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the acute decompensated heart failure national registry (ADHERE). Am Heart J 2005; 149: 209-216.
[20] Zannad F, Mebazaa A, Juilliere Y, Cohen-Solal A, Guize L, Alla F, Rouge P, Blin P, Barlet MH, Paolozzi L, Vincent C, Desnos M and Samii K. Clinical profile, contemporary management and one-year mortality in patients with severe acute heart failure syndromes: the EFICA study. Eur J Heart Fail 2006; 8: 697-705.
[21] Lam CS, Roger VL, Rodeheffer RJ, Bursi F, Borlaug BA, Ommen SR, Kass DA and Redfield MM. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. Circulation 2007; 115: 1982-1990.
[22] Levy D, Anderson KM, Savage DD, Kannel WB, Christiansen JC and Castelli WP. Echocardiographically detected left ventricular hypertrophy: prevalence and risk factors. The framingham heart study. Ann Intern Med 1988; 108: 7-13.
[23] Dwyer EM, Asif M, Ippolito T and Gillespie M. Role of hypertension, diabetes, obesity, and race in the development of symptomatic myocardial dysfunction in a predominantly minority population with normal coronary arteries. Am Heart J 2000; 139: 297-304.
[24] Buch J. Urapidil, a dual-acting antihypertensive agent: current usage considerations. Adv Ther 2010; 27: 426-443.
[25] van Veldhuisen DJ, Linssen GC, Jaarsma T, van Gilst WH, Hoes AW, Tijssen JG, Paulus WJ, Voors AA and Hillege HL. B-type natriuretic peptide and prognosis in heart failure patients with preserved and reduced ejection fraction. J Am Coll Cardiol 2013; 61: 1498-1506.
[26] Jhund PS, Anand IS, Komajda M, Claggett BL, McKelvie RS, Zile MR, Carson PE and McMurray JJ. Changes in N-terminal pro-B-type natriuretic peptide levels and outcomes in heart failure with preserved ejection fraction: an analysis of the I-preserve study. Eur J Heart Fail 2015; 17: 809-817.
[27] Yoshimura K, Kadoyama K, Sakaeda T, Sugino Y, Ogawa O and Okuno Y. A survey of the FAERS database concerning the adverse event profiles of alpha1-adrenoreceptor blockers for lower urinary tract symptoms. Int J Med Sci 2013; 10: 864-869.
[28] Elkayam U, Bitar F, Akhter MW, Khan S, Patrus S and Derakhshani M. Intravenous nitroglycerin in the treatment of decompensated heart failure: potential benefits and limitations. J Cardiovasc Pharmacol Ther 2004; 9: 227-241.
[29] den Uil CA and Brugts JJ. Impact of intravenous nitroglycerin in the management of acute decompensated heart failure. Curr Heart Fail Rep 2015; 12: 87-93.