Efficacy and Safety of Intravenous Urapidil for Older Hypertensive Patients with Acute Heart Failure: A Multicenter Randomized Controlled Trial

Wei Yang[1], Yu-Jie Zhou[2], Yan Fu[3], Jian Qin[4], Shu Qin[5], Xiao-Min Chen[6], Jin-Cheng Guo[7], De-Zhao Wang[8], Hong Zhan[9], Jing Li[4], Jing-Yu He[10], and Qi Hua[4]

[1]Department of Geriatrics, Xuanwu Hospital, Capital Medical University, Beijing;
[2]Department of Cardiology, An Zhen Hospital affiliated with Capital Medical University, Beijing;
[3]Fu Yan Emergency Department, Tong Ren Hospital affiliated with Capital Medical University, Beijing;
[4]Department of Cardiology, Xuanwu Hospital, Capital Medical University, Beijing;
[5]Department of Cardiology, First Hospital affiliated with Chongqing University, Chongqing;
[6]Department of Cardiology, Ningbo First Hospital, Ningbo;
[7]Department of Cardiology, Luhe Hospital of Beijing Tongzhou District, Beijing;
[8]Department of Cardiology, Mentougou District Hospital of Beijing City, Beijing;
[9]Emergency Department, First Hospital affiliated with Sun Yat-sen University, Guangzhou;
[10]Emergency Department, Xuanwu Hospital, Capital Medical University, Beijing, China.

Purpose: Urapidil is putatively effective for patients with hypertension and acute heart failure, although randomized controlled trials thereon are lacking. We investigated the efficacy and safety of intravenous urapidil relative to that of nitroglycerin in older patients with hypertension and heart failure in a randomized controlled trial.

Materials and Methods: Patients (>60 y) with hypertension and heart failure were randomly assigned to receive intravenous urapidil (n=89) or nitroglycerin (n=91) for 7 days. Hemodynamic parameters, cardiac function, and safety outcomes were compared.

Results: Patients in the urapidil group had significantly lower mean systolic blood pressure (110.1±6.5 mm Hg) than those given nitroglycerin (126.4±8.1 mm Hg, p=0.022), without changes in heart rate. Urapidil was associated with improved cardiac function as reflected by lower N terminal-pro B type natriuretic peptide after 7 days (3311.4±546.1 ng/mL vs. 4879.1±325.7 ng/mL, p=0.027) and improved left ventricular ejection fraction (62.2±3.4% vs. 51.0±2.4%, p=0.032). Patients given urapidil had fewer associated adverse events, specifically headache (p=0.025) and tachycardia (p=0.004). The one-month rehospitalization and all-cause mortality rates were similar.

Conclusion: Intravenous administration of urapidil, compared with nitroglycerin, was associated with better control of blood pressure and preserved cardiac function, as well as fewer adverse events, for elderly patients with hypertension and acute heart failure.

Key Words: Urapidil, hypertension, acute heart failure, randomized controlled trial

INTRODUCTION

Acute heart failure (AHF), either with reduced ejection fraction (HFrEF) or with preserved ejection fraction (HFpEF), remains an important cause of morbidity and mortality globally, especially for older adults, despite recent advances in treatment.[1-3] Moreover, there is increasing evidence that the prevalence of AHF is substantial in older adult patients complicated with hypertension, although evidence-based treatment strategies are generally lacking.[4] The development of novel pharmacologic agents for patients with both hypertension and AHF is urgently needed.

Long-term overload of the heart caused by elevated afterloading is a major clinical characteristic of hypertensive patients, particularly older adults. These patients typically exhibit reduced cardiac reserve and are therefore vulnerable to decompensated AHF after acute stimulus.[5] There is clinical evidence that the hemodynamic characteristics of AHF patients may be somewhat different from those with chronic heart failure.[6] 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.[7,8]

Vasodilators have been accepted as the first-line treatment for patients with hypertension and AHF,[9-11] and nitroglycerin is the vasodilator most often administered. However, adverse effects associated with nitroglycerin, such as headache, flushing, and reflective tachycardia, can limit its use,[12,13] and no obvious benefits to cardiac systolic and diastolic function have been confirmed.[12]

Urapidil, a sympatholytic antihypertensive drug with cardioprotective effects exerted through the peripheral alpha-adrenergic receptor and via central 5-hydroxytryptamine (serotonin) receptor 1A (HTR1A) agonistic action may have great therapeutic potential for older patients with hypertension and AHF.[14,15] However, evidence from randomized controlled trials concerning this medication is limited.

In the present study, we evaluated the efficacy and safety of intravenous urapidil for older hypertensive patients with AHF (both HFrEF and HFpEF) relative to that of conventional vasodilator nitroglycerin. In particular, we performed a post-hoc subgroup analysis of the role of intravenous urapidil on left ventricular function in patients with HFpEF.

MATERIALS AND METHODS

This study is part of a multicenter clinical trial that was performed in 11 research centers in mainland China. The Ethics Committees of the included research centers approved the protocols of the study before its performance, and all the in-cluded patients and their relatives signed informed consent forms. The protocol of the clinical trial was registered in the Chinese Clinical Trial Registry (ChiCTR-TRC-11001781) before enrollment of the first patients. A subgroup portion of the current study, which included only AHF patients with diabetes, has been published previously.[16]

Patients and study protocol

This study was designed as an open-label randomized controlled trial to evaluate the efficacy and safety of intravenous urapidil relative to conventional vasodilator nitroglycerin for older hypertensive patients. These patients had also received diagnoses of AHF, and included patients with HFrEF and those with HFpEF. Enrollment occurred from August 1, 2011 to November 30, 2013. The included patients were randomly assigned via random number generation from a computer to either an urapidil-based treatment group (n=89) or a nitroglycerin-based control group (n=91). The group assignment of the patients was known to both the investigators and the participants.

Inclusion and exclusion criteria of the patients

Patients were included in the current study if they fulfilled all of the following criteria: aged >60 years; previous diagnosis of hypertension, defined as systolic blood pressure (SBP) >140 mm Hg or diastolic blood pressure (DBP) of >90 mm Hg, or regularly taking antihypertensives in accordance with the 2010 Chinese guidelines for the management of hypertension;[17] received a diagnosis of AHF, including either HFrEF or HFpEF, according to the 2014 Chinese guidelines for the diagnosis and treatment of heart failure;[18] and scheduled for inpatient treatment in the included medical centers. A diagnosis of AHF was mainly based on clinical manifestations (staged above Class II of the New York Heart Association Classification), observations on physical examination, and echocardiographic results.

Patients were excluded from the current study if they had any of the following: contraindications for intravenous administration of vasodilators, such as cardiogenic shock, SBP ≤100 mm Hg, cerebral ischemia, or severe stenosis of the carotid arteries; confirmed acute coronary syndrome; severe structural heart disease comorbidities, including severe valvular stenosis, hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, or pericarditis; any severe condition involving other systems or organs, such as severe chronic asthmatic bronchial and pulmonary disease, severe liver dysfunction [>3-fold maximum normal values of alanine aminotransferase (ALT) and aspartate aminotransferase (AST)], or kidney insufficiency (>2-fold maximum normal value of creatinine); known or suspected allergy to any of the tested medications and their ingredients; end-stage disease as determined by researchers (e.g., cancer cachexia or severe mental illness); received the tested medications within 60 days before enrollment; or past or present involvement in other clinical research programs.

Medications and dosage titration methods

All the included patients were allowed to continue use of regular antihypertensives (including calcium-channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and diuretics) and intake of other cardiovascular medications (digoxin, amiodarone, and statins) during the study. Beta-blockers, which may confer an increased risk of deterioration of AHF, were not prescribed during the study period.

For patients assigned to the urapidil group, intravenous urapidil hydrochloride (Ebrantil, Byk Gulden, Konstanz, Germany; every 100 mg of urapidil diluted in 50 mL of normal saline) was continuously administered, and the dosages of the urapidil were adjusted according to the blood pressure of the patients. Generally, the administration of urapidil began at a small dose, depending on the clinical situation, and then gradually increased to the target dose (50 to 100 µg/min) within 6 h, with a maximum dose of 400 µg/min. Intravenous urapidil was discontinued if the SBP was <90 mm Hg. However, if the symptoms of AHF were not relieved during the first 48 hours after the start of urapidil administration, it was discontinued and subsequent treatment was based on the judgment of the investigators.

For patients assigned to the nitroglycerin group, intravenous nitroglycerin (Beijing Yimin Pharmaceutical, Beijing, China; every 10 mg of nitroglycerin diluted in 50 mL of 5% glucose solution) was continuously administered. The starting dose of nitroglycerin began at a small dose, depending on the clinical situation, and then increased to the target dose (5 to 10 µg/min) within 6 h, with a maximum dose of 40 µg/min. The protocol for dosage adjustment and the criteria for the discontinuation of nitroglycerin were the same as for intravenous urapidil. Only patients who received the tested medications for more than 24 hours were included for subsequent analyses.

Outcomes of interest

Each patient in the study underwent repeated assessment of hemodynamic parameters (i.e., heart rate, SBP, and DBP) at hospital admission (baseline) and after 1, 2, 3, and 7 days of intravenous vasodilator administration. Serum levels of N-terminal B type natriuretic peptide (NT-proBNP) were also evaluated at the same time points. Transthoracic echocardiography was performed to evaluate the systolic function of the left ventricles of the included patients, and the left ventricular ejection fraction (LVEF) and left ventricular end-diastolic volume (LVEDV) were also measured at hospital admission and 2 and 7 days after intravenous vasodilator administration. Serum parameters reflective of lipid levels and glucose metabolism and hepatic and renal functions were also evaluated at hospital admission and 2 and 7 days after intravenous vasodilator administration. No other intravenous vasodilators were used during this period.

The patients were followed for 1 month after discharge from the hospital. Clinical outcomes were evaluated for patients from each group, including heart failure-related rehospitalization, as well as all-cause mortality. We also investigated the rates of medication-related adverse events during the treatment periods, specifically headache, flushing, tachycardia, and hypotension.

Echocardiographic evaluation of left ventricular function

Global left ventricle function was assessed by transthoracic echocardiography (Philips IE-33 Ultrasonic System, Philips, Amsterdam, the Netherlands). The apical 2- and 4-chamber views were chosen for the measurement of LVEF, used as an index of global left ventricular systolic function. To calculate LVEF, end-diastolic and end-systolic frames were selected, end-diastolic and end-systolic endocardial borders were manually traced, and biplane LVEF was calculated. LVEDV was also measured for each patient.

Statistical analyses

The calculation of sample size was based on the previous findings of a pilot study, in which the difference in LVEF after urapidil therapy, as compared with those who received nitroglycerin, was 8% with a combined standard error (SE) of 16%. Assuming that the efficacy for the testing of type 1 error α=0.05 and the efficacy for the testing of type 2 error β=0.10, then the calculated sample size n in each group was:

$$n=2\times[(1.96+1.282)\times SE/minimax\ design]^2=2\times[(1.96+1.282)\times 16/8]^2=84.$$

Considering the potential loss of patients during the follow-up, the study was designed so that each group comprised 90 patients. Continuous data are presented as mean±standard deviation, and the categorical data are presented as numbers and frequencies. Each set of data was tested for normal distribution. Differences in the continuous and categorical data between the two groups were analyzed using Student's t-test or chi-squared analysis. Differences in the data at multiple time points between the two groups were analyzed using repeated-measures analysis of variance (ANOVA) and an independent-samples t-test. Statistical analyses were conducted with SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). A p value<0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the included patients

In this study, 180 patients with both hypertension and AHF were enrolled from 11 medical centers in mainland China. Each center contributed 15−20 patients (Table 1). The ages of the patients varied from 60 to 88 years. In the urapidil group, the mean age was 77.5 years, with 51 men and 38 women. In the nitroglycerin group, the mean age was 76.9 years, with 54 men and 37 women.

The patients of the two groups were similar for demographic and clinical factors, such as age and gender, the duration of hypertension, manifestations of AHF (as evaluated by LVEF and distribution of New York Heart Association classifications), baseline renal function [as evaluated by the estimated glomerular filtration rate (eGFR)], comorbidities of coronary heart disease, diabetes mellitus, and atrial fibrillation, and cardiovascular medications, such as antihypertensives and digoxin (all *p*>0.05). All of the included patients received the predetermined dosages of intravenous vasodilators in accordance with the assigned protocols. The mean treatment duration for nitroglycerin was 89 h, and the mean dosage was 86.4 mg per patient. The mean treatment duration for urapidil was 88 h, and mean dosage was 412.9 mg per patient.

Overall, 70 patients with HFpEF were included in the current analysis, of which 34 were randomized to the nitroglycerin group, while 36 were assigned to the urapidil group (Supplementary Table 1, only online). The patients with HFpEF assigned to the two groups were balanced for baseline characteristics, including gender, age, duration of hypertension, baseline LVEF and NT-proBNP, New York Heart Association classifications, and the antihypertensives used (*p*>0.05).

SBP, DBP, and heart rate

Repeated-measures ANOVA and results of multivariate analysis of the intra-group elements showed that in both the urapidil and nitroglycerin groups, 7 days of treatment were associated with significantly lower SBP (F=91.6), DBP (F=32.5), and heart rate (F=26.6) across the different time points (Fig. 1).

Regarding SBP (Fig. 1A), in patients of the urapidil group, reductions in SBP were observed after 1, 2, 3, and 7 days of treatment, and for those in the nitroglycerin group, reduced SBP also occurred within 7 days. However, at days 3 and 7, the mean SBPs of the urapidil group (126.3±5.2 and 110.1±6.5 mm Hg, respectively) were significantly lower than those of the nitroglycerin group (138.3±4.1 and 126.4±8.1 mm Hg; *p*=0.045, 0.022).

Regarding DBP and heart rate, the reductions in both groups

Table 1. Baseline Characteristics of the Hypertensive Patients in the Nitrlycerin and Urapidil Groups*

Index	Nitroglycerin	Urapidil	*p* value
Patients (n)	91	89	0.456
Male (n, %)	54 (59.3)	51 (57.3)	0.423
Age (yr)	76.9±11.3	77.5±5.3	0.701
Duration of hypertension (yr)	23.1±3.2	24.0±1.9	0.321
HGB (g/L)	107.0±4.2	106.7±4.6	0.341
eGFR (mL/min)	45.2.0±4.8	44.0±4.1	0.319
HFrEF (n, %)	57 (62.6)	53 (59.6)	0.142
HFpEF (n, %)	34 (37.4)	36 (40.4)	0.421
LVEF (%)	36.2±4.2	37.1±4.2	0.243
NYHA classification (n, %)			
Class II	39 (42.8)	39 (43.8)	0.654
Class III	42 (46.2)	41 (46.1)	0.754
Class IV	10 (11.0)	9 (10.1)	0.565
Comorbidities (n, %)			
CHD	27 (29.7)	26 (29.2)	0.867
DM	47 (51.6)	43 (48.3)	0.646
AF	25 (27.5)	26 (29.2)	0.567
Number of antihypertensives (n, %)			
1	35 (38.5)	34 (38.2)	0.657
2	45 (49.4)	43 (48.3)	0.765
3	11 (12.1)	12 (13.5)	0.567
Concurrent CV medications (n, %)			
CCBs	40 (44.0)	38 (42.7)	0.347
ACEIs/ARBs	47 (51.6)	49 (55.1)	0.245
β-blockers	38 (41.8)	36 (40.4)	0.364
Diuretics	59 (64.8)	57 (64.0)	0.432
Digoxin	25 (27.5)	24 (27.0)	0.381

HGB, hemoglobin; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, the New York Heart Association; CHD, coronary heart disease; DM, diabetes; AF, atrial fibrillation; CV, cardiovascular; CCBs, calcium-channel blockers; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.
*Reported as mean±standard deviation, unless indicated otherwise.

within the 7 days were statistically similar (Fig. 1B and C). These results indicated that, relative to nitroglycerin, urapidil was associated with better-controlled blood pressure, as reflected by the significantly decreased SBP after 3 and 7 days of treatment. However, this effect was not accompanied by a significant difference in heart rates between the two treatments.

Cardiac systolic function

Repeated-measures ANOVA and results of multivariate analysis of the intra-group elements showed that, in both the urapidil and nitroglycerin groups, serum NT-proBNP levels (F=21.7) were significantly lower at the end of 7 days of treatment (Fig. 2A). The trends in reductions of serum NT-proBNP were similar at each time point, reaching a significant difference at day 7. That is, on day 7, serum levels of NT-proBNP of the urapidil group (3311.4±546.1 ng/mL; F=13.1) were significantly lower than that of the nitroglycerin group (4879.1±325.7 ng/mL; p=0.027). These results indicate that urapidil may be more effective in improving cardiac function than nitroglycerin for older patients with hypertension and AHF.

Patients in both groups had similar LVEFs and LVEDVs at admission and 2 days after the start of the respective vasodila-

tor treatments (Fig. 2B and C). After 7 days, the LVEF of patients in the urapidil group (62.2±3.4%) was significantly higher than that of patients given nitroglycerin (51.0±2.4%, p=0.032) (Fig. 2B). This suggests that the effects of urapidil were more favorable than those of nitroglycerin on left ventricular function. Seven days after the start of treatment, the mean LVEDV of the urapidil group (145.2±13.4 mL) was significantly lower than that of the nitroglycerin group (167.6±11.2 mL, p=0.024) (Fig. 2C). These data also support that the effect of intravenous urapidil on cardiac systolic function is more favorable for older patients with hypertension and AHF, compared with the conventional vasodilator nitroglycerin.

As for patients with HFpEF, although no significant differences in NT-proBNP were detected between patients from the two groups at 1 or 2 days after treatment, patients assigned to the urapidil group had significantly lower serum NT-proBNP at 3 days (4127.3±256.5 ng/mL vs. 5136.6±251.5 ng/mL, p=0.04) (Supplementary Table 2, only online) and 7 days after treatment (3256.4±237.4 ng/mL vs. 4534.2±35.4 ng/mL, p=0.02) (Supplementary Table 2, only online), compared to those treated with nitroglycerin. However, no significant differences in LVEF were detected between patients from the two groups
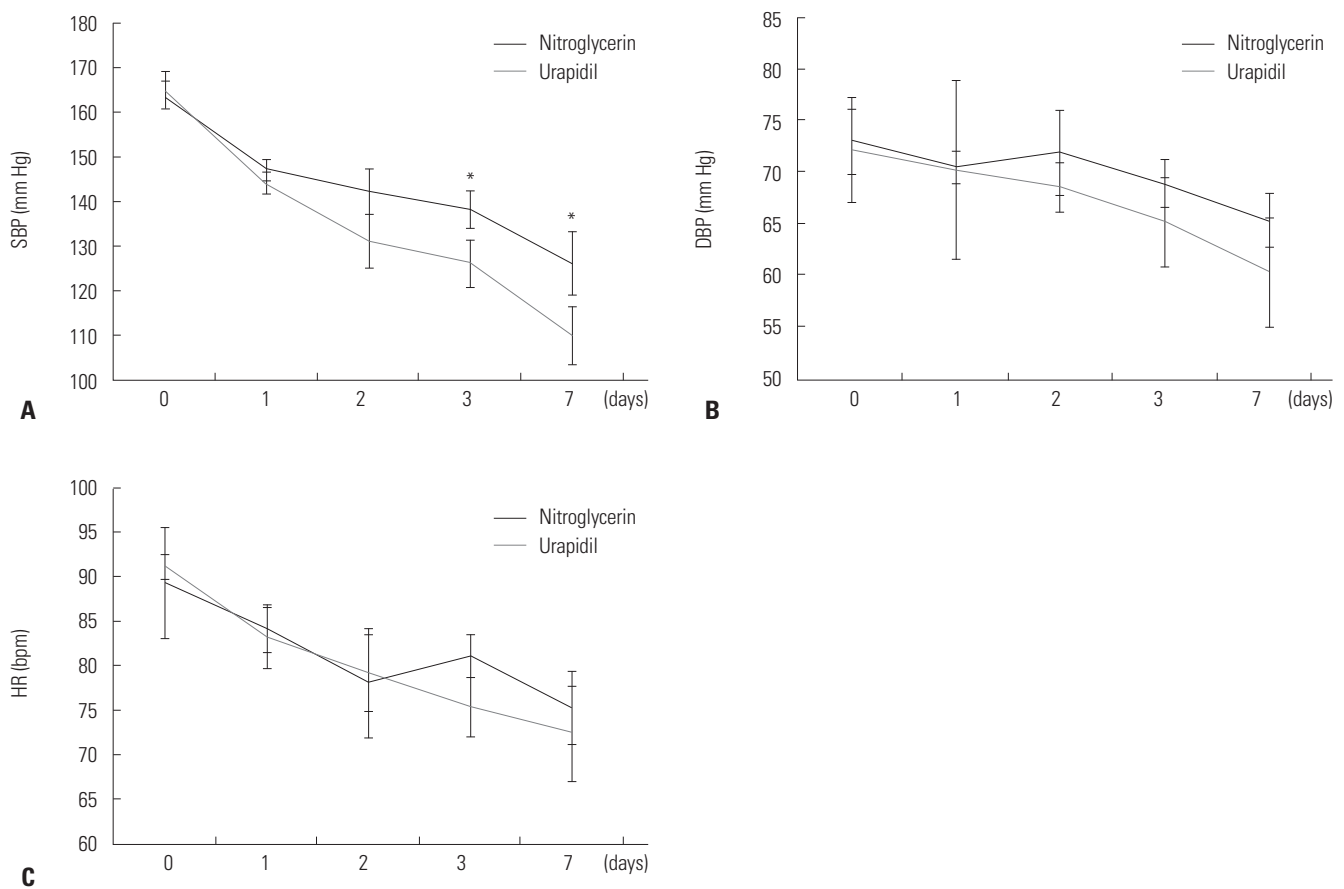

Fig. 1. Effects of intravenous urapidil and nitroglycerin on SBP (A), DBP (B), and heart rate (HR) (C) within 7 days after start of treatment for older patients with hypertension and AHF. *p<0.05 between the treatment groups at the indicated time point. SBP, systolic blood pressure; DBP, diastolic blood pressure; AHF, acute heart failure.

within 7 days after treatment ($p>0.05$, all; Supplementary Table 2, only online).

Biochemical indices of renal and liver function, blood lipids, and glucose metabolism

No significant changes, in either the urapidil or nitroglycerin group, were observed in serum indicators of renal function (eGFR), hepatic function (AST and ALT), blood lipids (triglycerides), or fasting plasma glucose during the 7 days after treatment (Table 2). This indicates that intravenous administration of urapidil, similar to the administration of nitroglycerin, is safe for older patients with hypertension and AHF.

Adverse events and clinical outcomes during follow-up

The vasodilator nitroglycerin is known for its adverse effects of headache and reflective tachycardia. In this study, urapidil was associated with fewer incidences of headache ($p=0.025$) and tachycardia ($p=0.004$), compared with nitroglycerin, al-

though flushing and hypotension were similar (Table 3). These results suggest that urapidil may be better tolerated by these patients.

At 1-month follow-up, the clinical outcomes of the two groups were not significantly different, specifically rates of hospitalization due to heart failure and all-cause mortality.

DISCUSSION

In this multi-center randomized controlled trial, we evaluated the efficacy and safety of intravenous urapidil relative to that of conventional vasodilator nitroglycerin in patients older than 60 years with hypertension and AHF. The results showed that urapidil was associated with better-controlled blood pressure within 7 days of the treatment period, and its benefits on SBP were not accompanied by a change in heart rate. The significantly lower serum NT-proBNP, increased LVEF, and reduced LVEDV of patients given intravenous urapidil, relative to the
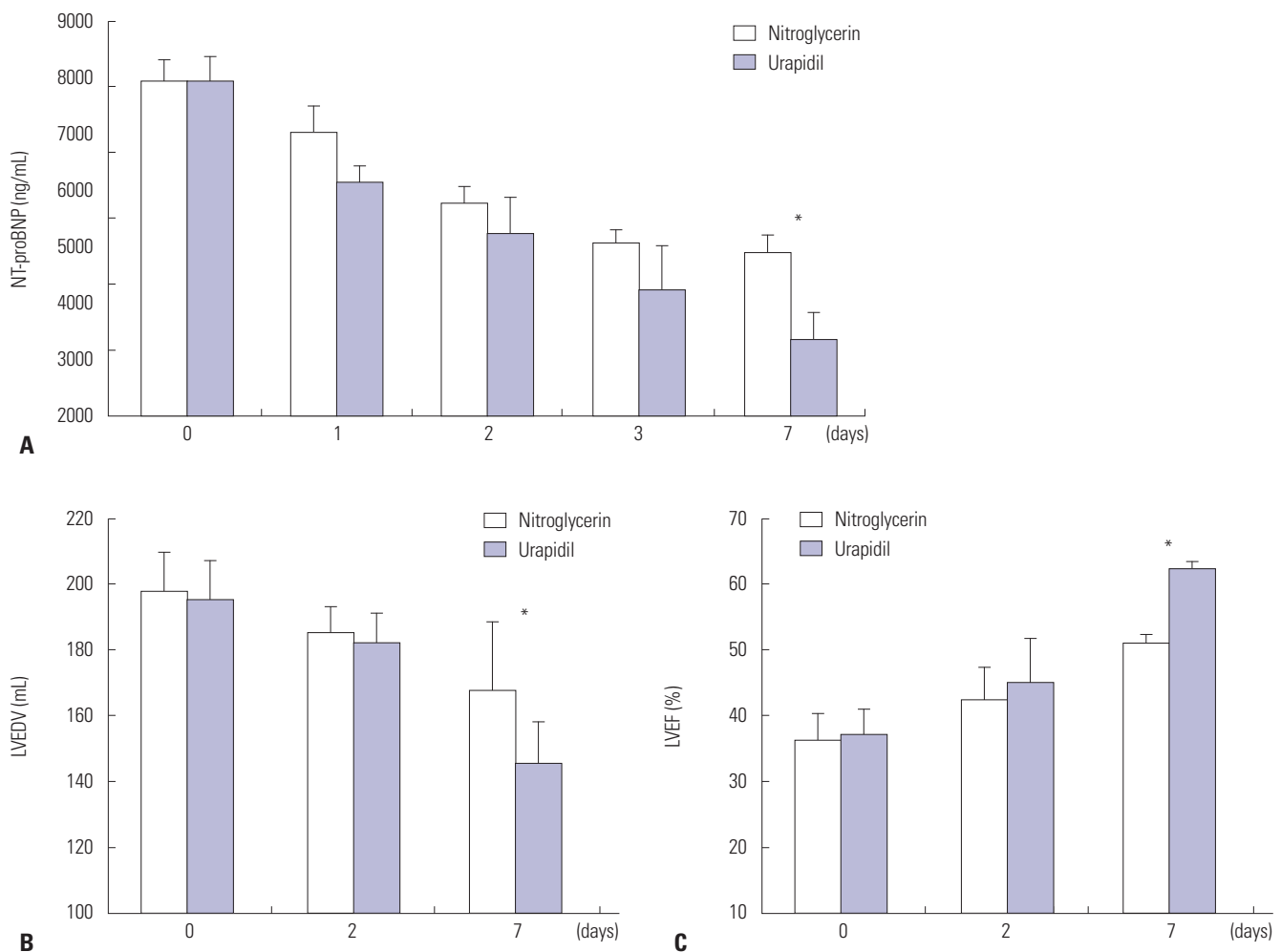

Fig. 2. Effects of intravenous urapidil and nitroglycerin on serum NT-proBNP (A), LVEF (B), and LVEDV (C) within 7 days after start of treatment for older patients with hypertension and AHF. *$p<0.05$ between the treatment groups at the indicated timepoint. LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; NT-proBNP, N-terminal B type natriuretic peptide.

Table 2. Effects of Urapidil on Serum Biochemical Indices: Comparison with Nitroglycerin*

Index	Urapidil			Nitroglycerin		
	Baseline	2 days	7 days	Baseline	2 days	7 days
ALT, IU/L	38.1±2.7	35.1±2.7	32.4±4.4	39.2±2.2	37.3±3.2	34.1±3.5
AST, IU/L	39.2±1.7	35.7±3.6	33.6±4.7	40.1±3.5	37.5±3.7	35.5±4.7
Creatinine, µmol/L	126.4±4.7	109.2±2.7	99.3±7.8	125.7±4.7	112.2±5.4	105.5±3.5
Fasting plasma glucose, mmol/L	7.4±4.7	6.7±2.2	6.3±1.4	7.5±1.4	7.0±1.2	6.3±1.5
Triglycerides, mmol/L	1.8±1.3	1.6±0.5	1.4±0.5	1.8±0.4	1.6±0.5	1.4±0.2

ALT, alanine aminotransferase; AST, aspartate aminotransferase.
*Reported as mean±standard deviation.

Table 3. Adverse Events within the Treatment Period and Clinical Outcomes during 1 Month Follow-Up: Comparison between the Urapidil and Nitroglycerin (Control) Groups

Index	Urapidil	Nitroglycerin	*p* value
Subjects, n	89	91	0.456
Adverse events			
Headache	0	7	0.025*
Flushing	0	3	0.252
Tachycardia	0	10	0.004*
Hypotension	1	3	0.628
Clinical outcomes			
Rehospitalization	33	39	0.523
Death	0	3	0.252

*Significant difference at the level of $p<0.05$.

nitroglycerin group, indicated better cardiac systolic function. Furthermore, results of the post-hoc analyses in patients with HFpEF indicated that urapidil treatment was associated with significantly lower NT-proBNP levels after 3 and 7 days of treatment, although LVEF was not significantly affected.

Intravenous urapidil showed no association with any impairment in renal or hepatic function, or disorders of blood glucose or lipid metabolism, and patients experienced fewer of the adverse events that are associated with other vasodilators, such as headache and tachycardia. Rehospitalization rates for AHF and all-cause mortality were not significantly different between the urapidil and nitroglycerin groups. Therefore, older hypertensive patients who suffer from AHF may receive more benefit from intravenous urapidil than nitroglycerin, indicated by the significantly more remarkable improvements in blood pressure and cardiac protective functions observed in this study. In addition, urapidil was safer and better tolerated in these patients.

Early clinical evidence confirmed the potential role of vasodilators in patients with AHF.[7,19] Pathophysiologically, AHF was defined as an acutely insufficient status of the heart after significant increases in pressure or fluid overloads or a severe dysfunction of the cardiovascular system. Dramatic increases in blood pressure, particularly SBP, have been recognized as an important component of the pathophysiologic process. Either as an initial cause or as an intermediate feature, hypertension can lead to pressure overload, which further impairs cardiac function. More importantly, constriction of the peripheral arteries seen in hypertension can cause poor perfusion in important organs, thereby inducing systematic manifestations in patients with AHF. Therefore, the benefits of vasodilators in these circumstances are obvious, since they could lead to a significant reduction of the afterload of the heart and improve the perfusion of the vital organs. Indeed, clinical evidence has also revealed the therapeutic role of vasodilators in hypertensive patients with AHF.[9,19] However, these results generally come from observational studies, and evidence-based therapy in AHF is lacking.[4,20] Indeed, although previous pilot trials, mostly from case reports or case series,[14,21] have suggested intravenous urapidil as a potential therapeutic option in patients with hypertension and AHF, randomized controlled trials are limited. In this study, we performed a multicenter randomized controlled trial to evaluate the efficacy of intravenous urapidil, compared with the clinically accepted vasodilator nitroglycerin, in older patients with hypertension and AHF. The results of our study, for the first time, to the best of our knowledge, indicated that intravenous urapidil may benefit old hypertensive patients that suffer from AHF by offering more remarkable blood pressure lowering and cardiac protective functions. Our results provided further evidence for the administration of urapidil in patients with hypertension and AHF.

Urapidil is proven to exert its antihypertensive action via both peripheral alpha-adrenergic receptor and central HTR1A antagonizing effects, which make it more effective for the regulation of afterload of the heart.[15] Furthermore, early observational studies with animals[22] and humans[23,24] indicated that urapidil could benefit cardiac output. However, the effects of urapidil on cardiac function have rarely been examined in randomized controlled trials. Our results indicated that, although both intravenous urapidil and nitroglycerin were effective in lowering blood pressure in older patients with hypertension and AHF, after 7 days of treatment those in the urapidil group achieved better-preserved cardiac systolic function. The mechanisms underlying the cardioprotective effects of urapidil in these patients, in our opinion, may not be fully explained by its beneficial effect on blood pressure. Indeed, a previous study of patients with coronary heart disease after coronary stenting showed that long-term urapidil may improve LVEF at midterm after coronary revascularization.[25] Some recent studies sug-

gested that urapidil treatment may improve myocardial function by increasing coronary flow and myocardial perfusion, thereby optimizing energy metabolism of the myocardium.[26]

Although our study was not designed to evaluate the role of urapidil in AHF patients with preserved LVEF, 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. Previous studies have indicated that serum NT-proBNP is of significant prognostic value in patients with HFpEF[27] and that a rise in NT-proBNP is associated with an increase in risk of adverse cardiovascular outcome (a fall was associated with a decrease in risk).[28] From this perspective, the present pilot study suggests that urapidil may be beneficial for AHF patients with HFpEF. It has to be mentioned that our study was not designed with adequate power to evaluate the potential benefits of urapidil in patients with HFpEF, and obviously, further studies are warranted.

An important issue concerning the use of current vasodilators is that they are often poorly tolerated by many AHF patients, due to headache, tachycardia, and flushing.[12,13] An important finding of the present study was that our older patients with AHF and hypertension were able to tolerate urapidil better than nitroglycerin, being less troubled by headache and tachycardia. Moreover, biochemical indices reflecting hepatic and renal function were not significantly changed after urapidil administration, which further confirmed its safety. Although the efficacy of urapidil failed to confer benefits in terms of improved rates of rehospitalization or mortality at the one-month follow-up, our study was not designed to evaluate these endpoints, and further studies with adequate statistical power are needed.

In conclusion, our study indicates that, for older adults with hypertension and AHF, intravenous administration of urapidil is associated with better control of blood pressure and preserved cardiac function, with fewer adverse side effects, compared to intravenous nitroglycerin. Further studies are warranted to evaluate whether treatment with urapidil in these patients is associated with improved clinical outcomes.

ACKNOWLEDGEMENTS

REFERENCES

1. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the european society of cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787-847.

2. Writing committee members, Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, et al. 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.

3. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation 2015;131:e29-322.

4. Alexander P, Alkhawam L, Curry J, Levy P, Pang PS, Storrow AB, et al. Lack of evidence for intravenous vasodilators in ED patients with acute heart failure: a systematic review. Am J Emerg Med 2015;33:133-41.

5. Cicci JD, Reed BN, McNeely EB, Oni-Orisan A, Patterson JH, Rodgers JE. Acute decompensated heart failure: evolving literature and implications for future practice. Pharmacotherapy 2014;34:373-88.

6. Felker GM, Adams KF Jr, Konstam MA, O'Connor CM, Gheorghiade M. The problem of decompensated heart failure: nomenclature, classification, and risk stratification. Am Heart J 2003;145(2 Suppl):S18-25.

7. Adams KF Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al. 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;149:209-16.

8. Zannad F, Mebazaa A, Juillière Y, Cohen-Solal A, Guize L, Alla F, et al. 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.

9. Piper S, McDonagh T. The role of intravenous vasodilators in acute heart failure management. Eur J Heart Fail 2014;16:827-34.

10. Levy PD, Laribi S, Mebazaa A. Vasodilators in acute heart failure: review of the latest studies. Curr Emerg Hosp Med Rep 2014;2:126-32.

11. Cherney D, Straus S. Management of patients with hypertensive urgencies and emergencies: a systematic review of the literature. J Gen Intern Med 2002;17:937-45.

12. Elkayam U, Bitar F, Akhter MW, Khan S, Patrus S, Derakhshani M. Intravenous nitroglycerin in the treatment of decompensated heart failure: potential benefits and limitations. J Cardiovasc Pharmacol Ther 2004;9:227-41.

13. den Uil CA, Brugts JJ. Impact of intravenous nitroglycerin in the management of acute decompensated heart failure. Curr Heart Fail Rep 2015;12:87-93.

14. Alijotas-Reig J, Bove-Farre I, de Cabo-Frances F, Angles-Coll R. Effectiveness and safety of prehospital urapidil for hypertensive emergencies. Am J Emerg Med 2001;19:130-3.

15. Buch J. Urapidil, a dual-acting antihypertensive agent: current usage considerations. Adv Ther 2010;27:426-43.

16. Yang W, Zhou YJ, Fu Y, Qin J, Qin S, Chen XM, et al. A multicenter, randomized, trial comparing urapidil and nitroglycerin in multifactor heart failure in the elderly. Am J Med Sci 2015;350:109-15.

17. Liu LS; Writing Group of 2010 Chinese Guidelines for the Management of Hypertension. [2010 Chinese guidelines for the management of hypertension]. Zhonghua Xin Xue Guan Bing Za Zhi 2011;39:579-615.

18. Chinese Society of Cardiology of Chinese Medical Association; Editorial Board of Chinese Journal of Cardiology. [Chinese guidelines for the diagnosis and treatment of heart failure 2014]. Zhonghua Xin Xue Guan Bing Za Zhi 2014;42:98-122.

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

93.

20. Mebazaa A, Longrois D, Metra M, Mueller C, Richards AM, Roessig L, et al. Agents with vasodilator properties in acute heart failure: how to design successful trials. Eur J Heart Fail 2015;17:652-64.

21. Wang RY, Chow JS, Chan KH, Pan HY, Wong RP. Acute haemodynamic and myocardial metabolic effects of intravenous urapidil in severe heart failure. Eur Heart J 1984;5:745-51.

22. Carlyle PF, Cohn JN. Systemic and regional hemodynamic effects of alpha-adrenoceptor blockade in chronic left ventricular dysfunction in the conscious dog. Am Heart J 1990;120:619-24.

23. Tebbe U, Wurst W, Neuhaus KL. Acute haemodynamic effects of urapidil in patients with chronic left ventricular failure. Eur J Clin Pharmacol 1988;35:305-8.

24. Zink M, Gombotz H, Wasler A, Grasser B, Rehak P, Metzler H. Urapidil reduces elevated pulmonary vascular resistance in patients before heart transplantation. J Heart Lung Transplant 2002; 21:347-53.

25. Kozàkovà M, Marco J, Heusch G, Bernies M, Bossi IM, Palombo C, et al. The alpha1-adrenergic blocker urapidil improves contractile function in patients 3 months after coronary stenting: a randomized, double-blinded study. Am Heart J 2004;147:E6.

26. Yao DK, Jia SQ, Wang L, Li HW, Zhang YC, Wang YL, et al. Therapeutic effect of urapidil on myocardial perfusion in patients with ST-elevation acute coronary syndrome. Eur J Intern Med 2009;20: 152-7.

27. van Veldhuisen DJ, Linssen GC, Jaarsma T, van Gilst WH, Hoes AW, Tijssen JG, et al. B-type natriuretic peptide and prognosis in heart failure patients with preserved and reduced ejection fraction. J Am Coll Cardiol 2013;61:1498-506.

28. Jhund PS, Anand IS, Komajda M, Claggett BL, McKelvie RS, Zile MR, et al. 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;17:809-17.