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Enhanced external counterpulsation (EECP) augmentation of amlodipine in elderly patients with isolated systolic hypertension (ISH) and wide pulse pressure: A comparative study

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Abstract: **Background**: Geriatric patients with isolated systolic hypertension (ISH) and wide pulse pressure (PP) were treated using enhanced external counter pulsation (EECP) combined with amlodipine versus amlodipine alone. **Objectives**: The efficacy of both treatment modalities was assessed based on hemodynamic parameters. **Methods**: Retrospectively included 132 elderly patients with ISH and wide PP in our hospital (Mar 2022-Jun 2024). After exclusion, 120 cases were analyzed and divided into the amlodipine group and the combined group. Primary indicators include endothelin-1 (ET-1), nitric oxide (NO), systolic blood pressure (SBP), PP, systemic vascular resistance (SVR), coronary flow reserve (CFR), flow-mediated vasodilatation (FMD); secondary measures include mean arterial pressure (MAP), wall shear stress (WSS) and adverse reaction incidence. **Results**: After 4 courses of treatment, patients in the combined group had significantly lower rates of ET-1, SBP, PP, MAP, SVR and the incidence of adverse reactions (all $P<0.05$); NO, FMD, WSS and CFR were higher (all $P<0.05$) than in the amlodipine group. **Conclusion**: EECP plus amlodipine has advantages over amlodipine monotherapy in treating elderly patients with ISH and wide PP, which provides a scientific basis for optimizing clinical treatment.

Keywords: Amlodipine; Enhanced external counterpulsation; Hemodynamics; Isolated systolic hypertension; Wide pulse pressure

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INTRODUCTION

The accelerated process of population aging has made the prevention and treatment of geriatric cardiovascular diseases a key priority in the global public health field. Among these conditions, isolated systolic hypertension (ISH) accounts for over 60% of cases in elderly hypertensive patients. What deserves greater attention is that approximately 75% of elderly ISH patients present with widened pulse pressure (PP) (Scott *et al*., 2021, Tsai *et al*., 2021). This pathological feature is directly associated with decreased vascular elasticity and aggravated atherosclerosis and has been proven to be an independent risk factor for cardio-cerebrovascular events and target organ damage. Clinical data indicate that the 5-year incidence of adverse cardiovascular events in elderly ISH patients with widened PP is 2.3 times higher than that in patients with essential hypertension. The therapeutic efficacy for this population directly impacts the quality of life and survival prognosis of the elderly. Therefore, there is an urgent clinical need for research on optimized treatment regimens targeting this specific group of patients (Egan *et al*., 2024, Brunstrom *et al*., 2023).

At present, clinical treatment for elderly ISH patients with widened PP still takes pharmacological intervention as the core. Among available medications, amlodipine—a dihydropyridine calcium channel blocker—has been recommended as a first-line agent due to its advantages including stable antihypertensive efficacy and favorable tolerability in elderly patients. Amlodipine exerts its effect by selectively inhibiting the transmembrane influx of calcium ions, thereby dilating peripheral arterioles and reducing peripheral vascular resistance, thereby achieving effective control of systolic blood pressure (Xie *et al*., 2021). However, the limitations of monotherapy with drugs have become increasingly prominent. On the one hand, elderly patients are often on polypharmacy regimens and the interactions between amlodipine and other medications may increase the risk of adverse reactions such as lower extremity edema and headache, leading to reduced treatment adherence in some patients. On the other hand, drug therapy primarily targets blood pressure values per se and has limited effects on improving impaired vascular endothelial function, vascular elasticity and hemodynamic disorders in elderly patients. In clinical practice, approximately 30% of elderly ISH patients with widened PP still experience unsatisfactory improvement in PP difference and insufficient coronary flow reserve (CFR) even after standard treatment with amlodipine (Gao *et al*., 2021, Hosseinzadeh *et al*., 2022). These issues make it difficult to effectively reduce the risk of long-term cardiovascular events, indicating that the single-drug treatment model can no longer meet the comprehensive therapeutic needs of this patient population.

Enhanced external counterpulsation (EECP), a non-invasive hemodynamic adjunctive therapy, offers a novel therapeutic approach for elderly patients with ISH and

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widened PP. Its core mechanism involves wearing inflatable cuffs on the lower extremities and buttocks. These cuffs are inflated synchronously during cardiac diastole to retrograde propel blood from the lower limbs into the aorta, thereby increasing aortic diastolic pressure and coronary perfusion pressure and improving myocardial blood supply. Meanwhile, rapid deflation during cardiac systole reduces peripheral vascular resistance and alleviates cardiac afterload, creating a counter pulsation effect (Abad Perez *et al*., 2022; Thomopoulos, 2023). In recent years, basic research has confirmed that EECP not only acutely modulates hemodynamic status but also stimulates vascular endothelial cells through sustained shear stress. This stimulation promotes the release of vasodilatory factors such as nitric oxide (NO) and inhibits the expression of vasoconstrictive substances like Endothelin-1 (ET-1). Consequently, EECP improves vascular endothelial function and delays the progression of atherosclerosis. EECP has demonstrated definite clinical value in the treatment of conditions such as chronic heart failure and coronary artery disease (Chopei *et al*., 2023). Its non-invasive, safe and well-tolerated properties make it particularly suitable for elderly patients with multiple comorbidities, laying a feasible foundation for its combined application with antihypertensive drugs.

Despite the increasingly widespread application of EECP in the treatment of cardiovascular diseases, systematic research on its combined use with amlodipine for elderly patients with ISH and widened PP remains relatively scarce (Xu *et al*., 2023). Existing studies have mostly focused on the blood pressure control efficacy of EECP in patients with essential hypertension, or analyzed the impact of monotherapy on patients with widened PP in isolation. There is a lack of multi-dimensional comparisons between combined therapy and monotherapy in terms of hemodynamic parameters, vascular endothelial function indicators and clinical safety (Jin, 2025, Rayegani *et al*., 2021). Particularly for the special population of elderly patients with ISH and widened PP, it remains unclear whether EECP can enhance the antihypertensive efficacy of amlodipine and reduce PP difference by improving vascular elasticity and blood perfusion and its synergistic mechanism of action and long-term safety have not been elucidated (Rezapour *et al*., 2022). This results in a lack of clear evidence for the clinical application of combined therapy. However, whether the vascular benefits of EECP can enhance the antihypertensive effects of amlodipine in elderly ISH patients with widened PP remains unclear. Existing studies do not provide comparative evidence on hemodynamics, endothelial function and clinical safety between monotherapy and combined therapy in this specific population.

Based on the aforementioned research background and knowledge gaps, this study enrolled elderly patients with ISH and widened PP as research subjects and designed a controlled trial comparing the combination therapy of EECP plus amlodipine versus amlodipine monotherapy (Xie *et al*., 2023). It aims to clarify the clinical advantages of the EECP-amlodipine combination regimen in the treatment of elderly ISH patients with widened PP, provide a scientific basis for optimizing the therapeutic strategy for this specific population, further reduce the risk of adverse cardio-cerebrovascular events and improve the prognosis of patients.

MATERIALS AND METHODS

General information

This study retrospectively selected ISH patients admitted to Hangzhou Gongshu District People's Hospital of Integrated Traditional Chinese and Western Medicine from March 2022 to June 2024, with the aim of comparing the effect of EECP combined with amlodipine with amlodipine alone to improve hemodynamic parameters. As shown in the flow chart of the experimental design in Fig. 1, a total of 132 patients' information was collected, 120 cases were analyzed after exclusion, which were categorized into a amlodipine group and a combined group in line with the treatment modality, with 60 cases in each group.

Inclusion criteria: (1) patients with ISH were diagnosed by the Chinese Journal of Hypertension July 2024 publication of the Chinese Guidelines for the Prevention and Control of Hypertension (2024 Revision) written by the Chinese Guidelines for the Prevention and Control of Hypertension Revision Committee(Wang, 2025); (2) a PP difference of >70 mmHg; (3) 60 years of age or older; (4) clinical data and relevant examinations were complete.

Exclusion criteria: (1) with speech, mental or psychological disorders; (2) heart failure; (3) stroke; (4) moderate to severe valvular disease; (5) chronic renal dysfunction; (6) chronic liver disease; and (7) thrombotic diseases and blood diseases.

Treatment methods

According to the medical records, both groups of patients received standardized basic management for hypertension during the treatment period. Based on the treatment regimens and doctor's orders documented in the medical records, the patients were divided into the amlodipine group and the combined treatment group.

Patients in the amlodipine group were given amlodipine treatment, amlodipine using amlodipine benzenesulfonate tablets, the initial dosage was set at 5 mg/day, capped at 10 mg/day. The patients received medication continuously for at least 24 weeks. All patients received an initial dose of 5 mg/day. If systolic blood pressure (SBP) was ≥ 130 mmHg after 2 weeks of treatment, the dose was increased to 10 mg/day.

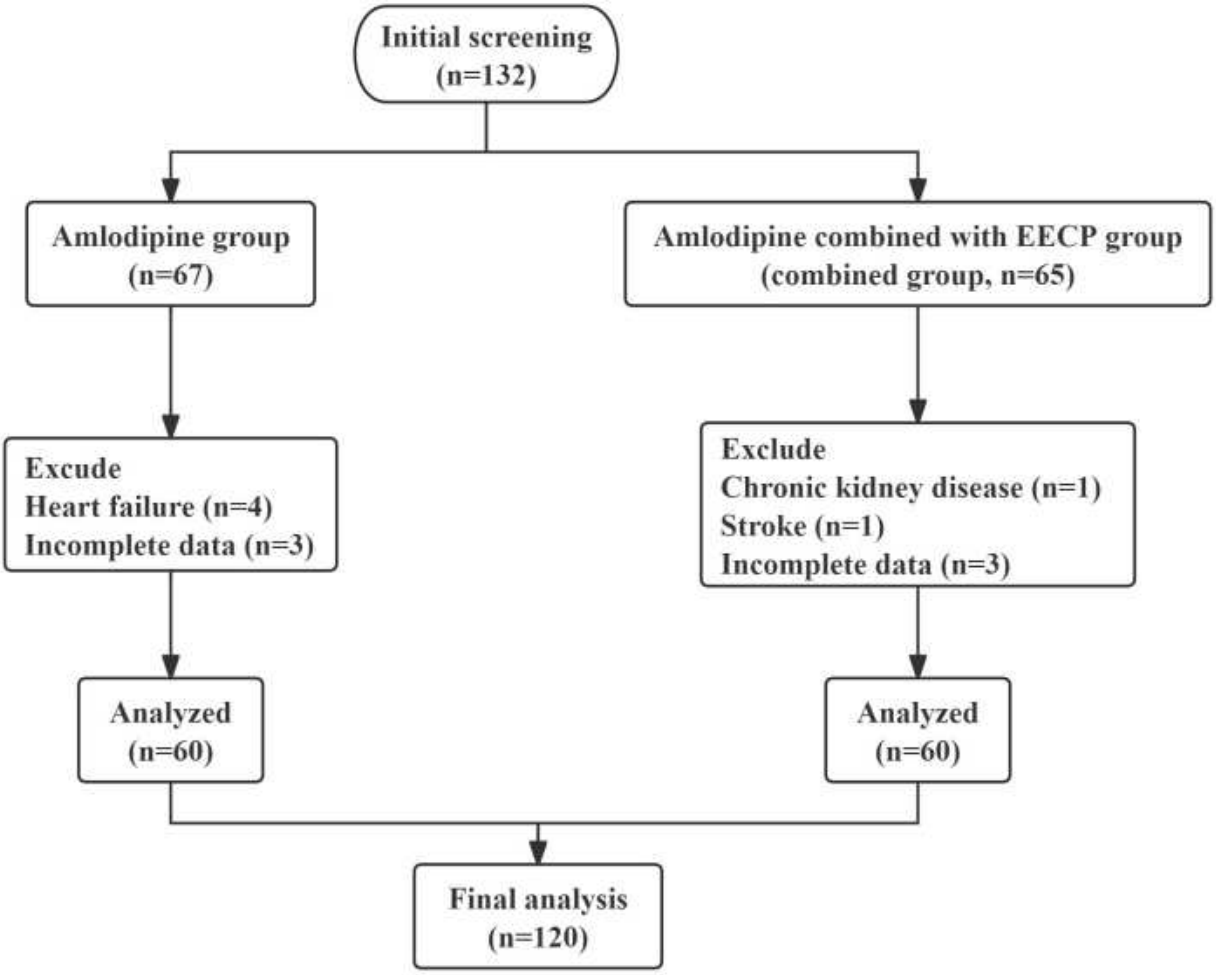

Fig. 1: Flowchart design

Patients in the combined group were treated with external counterpulsation on the basis of the amlodipine group. EECP was performed using a balloon type external counterpulsation device and the external counterpulsation treatment program was performed 35 one-hour sessions over 6 weeks, a total of four treatment courses were conducted. The EECP treatment protocol in this study strictly adheres to the Expert Consensus on Clinical Application of Enhanced Extracorporeal Counterpulsation (2023 Version)(Branch, 2024), with clear core operational details and standardized implementation. The inflation pressure of the airbag was set individually, adjusted based on the patient's lower limb circumference (0.05–0.06 MPa for thigh circumference > 50 cm, 0.04–0.05 MPa for < 50 cm) and subjective tolerance, with the criterion of no obvious pain. Synchronization triggering used the R wave of the electrocardiogram as the signal: inflation occurred 50 ms after the peak of the R wave and deflation occurred 30 ms before the end of the T wave, with a synchronization accuracy error ≤ 10 ms. Calibration was performed before each treatment session. Before treatment, the ankle-brachial index was measured to rule out contraindications. During treatment, heart rate and blood pressure were automatically recorded every 5 minutes and the patient's feelings were assessed every 10 minutes. After treatment, vital signs and skin condition were rechecked. Protocol adjustments were based on symptoms and indicators: if leg pain occurred (visual analog scale score ≥ 3), the pressure was reduced by 0.01 MPa; if blood pressure fluctuated > 160/< 110 mmHg, treatment was paused. All operators held dual certifications, received 2 weeks of standardized training and passed an assessment (pass rate ≥ 95%) before performing independent operations. A two-person verification system and monthly quality spot checks were adopted to ensure operational consistency (Cao *et al*., 2024).

In this study, patients in neither of the two groups were hospitalized continuously for 24 weeks. The entire course of diagnosis and treatment mainly consisted of outpatient day-care monitoring and short-term hospitalization when necessary; short-term hospitalization was only arranged for patients to observe treatment effects when they experienced severe blood pressure fluctuations or serious adverse reactions.

Observation indicators

ET-1 and NO

As documented in the medical record data, procoagulant tubes were used to collect 5 mL of fasting venous blood from patients as test samples and after centrifugation at 3000 r/min for 10 min, the serum portion was separated, with the enzyme immunization kit for serum ET-1 and serum NO. All serological test data were extracted from medical records.

SBP, PP and mean arterial pressure (MAP)

SBP and diastolic blood pressure (DBP) were measured using the electronic sphygmomanometer and PP and MAP were calculated. All data were extracted from medical records.

Systemic vascular resistance (SVR), CFR, flow mediated dilation (FMD) and wall shear stress (WSS)

CFR refers to the ratio of coronary blood flow in the state of maximum vascular dilation to that at rest. It is a core indicator for evaluating the reserve function of the coronary circulation(Wang *et al*., 2023).

FMD refers to the endothelium-dependent vasodilation response of peripheral arteries (the brachial artery is commonly used) triggered by blood flow reperfusion after a brief period of blood flow occlusion. It is a classic non-invasive indicator for assessing vascular endothelial function (Yin *et al*., 2023).

WSS refers to the tangential frictional force exerted on the inner wall of blood vessels when blood flows (Li *et al*., 2024).

SVR refers to the total resistance encountered by blood when flowing through the systemic peripheral blood vessels. It is a core hemodynamic indicator reflecting the vasomotor state of peripheral blood vessels (Li *et al*., 2025).

FMD, WSS and CFR can be assessed using a color Doppler ultrasound. SVR is calculated from MAP and CO. All echocardiography data were extracted from medical records.

Incidence of adverse effects during treatment

In this study, EECP combined with amlodipine versus amlodipine alone was used to treat ISH in wide-pulse-pressure elderly patients and the adverse effects mainly included tachycardia, nausea and vomiting and dizziness and headache (Yang *et al*., 2022).

Based on a retrospective design, the adverse event monitoring data of this study were all obtained from the electronic medical record system of XXX Hospital. During the treatment period, medical staff conducted real-time monitoring through inquiries and physical examinations. Adverse events were classified into grades 1 to 4 according to their severity and the management measures for adverse events in each group were specified based on medical record records, as detailed below; Grade 1 (Mild): Mild symptoms that do not affect daily life or treatment and resolve spontaneously without special intervention (e.g., transient dizziness, mild leg soreness); Grade 2 (Moderate): Obvious symptoms that cause slight interference with daily life but are tolerable, requiring symptomatic treatment (e.g., persistent nausea, leg pain affecting walking); Grade 3 (Severe): Severe symptoms that are intolerable, requiring treatment suspension and active intervention (e.g., severe tachycardia with chest tightness, large-area skin bruising); Grade 4 (Life-threatening): Fatal adverse events requiring emergency rescue.

The management methods for specific adverse events are as follows:

1. Tachycardia (Grades 1-2):

If the heart rate is < 110 beats per minute, the patient is advised to lie flat and rest, reduce activity and no adjustment to medication dosage is needed.

If the heart rate is ≥ 110 beats per minute (Grade 2), metoprolol 12.5 mg is administered orally temporarily once a day and discontinued after the heart rate stabilizes.

2. Nausea (Grades 1-2):

Patients are instructed to take medications after meals to avoid fasting; meanwhile, vitamin B6 20 mg is administered orally three times a day.

3. Dizziness (Grades 1-2):

Blood pressure is monitored. If the systolic blood pressure is > 110 mmHg, the patient is advised to change body positions slowly. If the systolic blood pressure is ≤ 110 mmHg, the dosage of amlodipine is appropriately reduced (Rodgers *et al*., 2024).

Sample size calculation methodology

The sample size of this study was determined through analysis using G*Power 3.1.9.7 computer software, aiming to identify the sample size required to detect statistically significant differences. The sample size calculation was based on the primary outcome measure of SBP. Referring to previous studies (Islam *et al*., 2025), a mean reduction of 20.9 mmHg in systolic blood pressure after treatment was considered clinically significant for patients aged over 55 years, with an estimated Cohen's d of 0.72. Setting the alpha level at 0.05 and statistical power at 95%, the calculation indicated that 52 patients per group were needed. Considering potential uncertainties, the final sample sizes for analysis in this study were determined as the amlodipine monotherapy group (n=60) and the combined treatment group (n=60), which we believe are sufficient to draw reliable conclusions.

Statistical analysis

Statistical analysis of the data was performed using SPSS 27.0 software. Propensity scores were used to control for confounding factors, with the nearest-neighbor matching method employed for propensity score matching (PSM)

and a matching tolerance of 0.02. After matching, the standardized mean difference (SMD) was used to evaluate the balance of baseline characteristics between groups, where an SMD < 0.1 indicated good balance. The Shapiro-Wilk test was used for normality testing of the data and the Levene test was used for homogeneity of variance testing. For continuous data that conformed to a normal distribution, paired t-tests were used for intra-group comparisons, independent-samples t-tests were used for inter-group comparisons and the data were expressed as mean ± standard deviation (mean ± SD). For continuous data that did not conform to a normal distribution: the data were expressed as median (interquartile range) [M (Q1, Q3)], Wilcoxon tests were used for intra-group comparisons and Mann-Whitney U tests were used for inter-group comparisons; additionally, Bonferroni correction was applied to the P-values. Categorical data were expressed as counts (percentages) [n (%)] and chi-square tests were used for inter-group comparisons. All statistical tests were two-tailed and a P-value < 0.05 was considered statistically significant.

Data collection

This study was a retrospective analysis. All data were centrally retrieved and extracted from the standardized medical data system of Hangzhou Gongshu District People's Hospital of Integrated Traditional Chinese and Western Medicine between March 2022 and June 2024. Patient demographic characteristics [age, gender, body mass index (BMI)], history of comorbidities (such as diabetes mellitus and hyperlipidemia), amlodipine medication regimens (dosage, adjustment records), inpatient/outpatient follow-up records and information on all adverse reactions (symptom type, onset time, treatment measures and outcomes) were obtained from the Electronic Medical Record system. Data on vasoactive biomarkers including ET-1 and NO before treatment and after 4 courses of treatment were extracted from the Laboratory Information System. Imaging data and analysis results related to CFR, FMD and WSS detected by echocardiography were collected from the Picture Archiving and Communication System. These data were independently interpreted by 2 ultrasonographers with intermediate professional titles or above and consistent results were adopted. For patients in the combined treatment group, EECP treatment parameters, number of treatment sessions and real-time monitored heart rate and blood pressure data during treatment were extracted from the special registration database for EECP treatment. Data on SBP, PP and MAP at each treatment node were collected from outpatient blood pressure monitoring records and patients' home blood pressure logs. SVR was calculated using the formula "(MAP - Central Venous Pressure) × 80 / Cardiac Output" combined with clinically measured indicators. All data were extracted and entered into an Excel database by 2 independent researchers. Quality control was conducted through cross-verification and review against original medical records. Discrepancies were discussed and confirmed by the research team before being included in the analysis, so as to ensure the accuracy and completeness of the data. The primary outcome measures of the study include SBP, PP, SVR, CFR, FMD, ET-1 and NO. The secondary outcome measures include the incidence of adverse reactions, MAP and WSS.

RESULTS

Comparison of baseline data between the two groups

In this retrospective cohort study, the patients' pretreatment characteristics were statistically analyzed and the control and combined groups were comparable, as no significant difference was found between them (Table 1).

Comparison of ET-1 and NO

As can be seen in table 2, during the first two courses of treatment, ET-1 levels did not change significantly in the combination group relative to the amlodipine group (P=0.235; P=0.553). The group receiving both the 3rd and 4th courses showed a larger decrease compared to the amlodipine group (P=0.025; P=0.015). After 3 courses of treatment, no significant alteration in NO levels was detected in the combination group compared to the amlodipine group (P=0.290; P=0.125; P=0.254). After 4 courses of treatment, significantly higher NO was noted in the combined group relative to the amlodipine group (P=0.021). It is suggested that EECP combined with amlodipine resulted in vasodilatation, increased blood flow, improved circulation and reduced vascular resistance in elderly patients with pure systolic hypertension with wide PP compared to amlodipine alone.

Comparison of SBP, PP and MAP between the two groups

As can be seen in table 3, after treatment, in the first 2 courses of treatment, compared with the amlodipine group, the patients in the combined group of these three indices showed nonsignificant changes (SBP: P=0.253; P=0.221; PP: P=0.105; P=0.124; MAP: P=0.095; P=0.541). After the 3rd and 4th courses of treatment, patients in the combined group showed a significant decrease in all three indices compared to the amlodipine group (SBP: P=0.015; P=0.022; PP: P=0.035; P=0.041; MAP: P=0.041; P= 0.040). From the above data, it can be seen that both amlodipine alone and EECP combined with amlodipine can reduce SBP, PP and MAP in patients and EECP combined with amlodipine has advantages in reducing SBP, PP and MAP in patients.

Comparison of SVR between the two groups

As can be seen in table 4, after treatment, SVR of the combined group in the first 3 courses was not significantly reduced (P=0.287; P= 0.214; P=0.285), the 4th course of treatment resulted in a significant reduction in SVR in the combined group compared to the amlodipine group (P=0.023).

Table 1: Baseline information of patients

Indicator	Amlodipine group (n=60)	Combined group (n=60)	95% CI		*P*	Effect size
			Lower	Upper		
Age (years)	68.73±6.08	67.18±4.88	-0.45	3.54	0.127	0.14
BMI (kg/m^2)	22.62±1.7	22.76±1.80	-0.77	0.49	0.662	-0.04
Gender						
Male	35	30	0.681	2.878	0.36	0.084
Female	25	30				
LVEF (%)	59.9±6.35	61.37±6.20	-3.74	0.80	0.203	-0.12
NT-proBNP (pg/mL)	261.53±17.59	257.7±17.83	-2.57	10.23	0.239	0.11
HR (bpm)	72.7±5.55	73.67±5.29	-2.93	0.99	0.331	-0.09
ALT (U/L)	33.75±1.94	33.97±2.02	-0.93	0.50	0.549	-0.06
AST (U/L)	33.93±1.87	33.87±1.75	-0.59	0.72	0.840	0.02
Creatinine (μmol/L)	82.33±5.91	80.34±7.40	-0.44	4.41	0.107	0.15
Fasting blood glucose (mmol/L)	6.1±0.45	6.03±0.49	-0.10	0.24	0.428	0.07
Total cholesterol (mmol/L)	5.44±0.65	5.29±0.55	-0.07	0.37	0.169	0.12
Triglycerides (mmol/L)	1.55±0.21	1.58±0.22	-0.10	0.05	0.492	-0.07
LDL (mmol/L)	2.45±0.29	2.41±0.33	-0.02	0.07	0.16	0.06
HDL (mmol/L)	1.34±0.03	1.35±0.03	-0.02	0.004	0.224	-0.16
Diabetes mellitus	13	14	0.386	2.142	0.827	-0.02
Amlodipine dosage						
5 mg	38	40	0.408	1.83	0.702	-0.035
10 mg	22	20				

Note: BMI: body mass index; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal brain natriuretic peptide precursor; HR: heart rate; ALT: alanine aminotransferase; AST: aminotransferase; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

Table 2: Comparison of ET-1 and NO ($\bar{x}\pm s$)

Indicator	Time	Mean±SD		95% CI		*P*	Effect size
		Amlodipine group(n=60)	Combined group(n=60)	Lower	Upper		
ET-1 (pg/mL)	Pre-treatment	75.66±10.31	75.79±9.95	-3.80	3.53	0.542	-0.01
	1 course	73.58±9.74	72.4±10.26	-2.48	4.75	0.235	0.06
	2 courses	70.36±9.47*	70.26±9.79*	-3.38	3.58	0.553	0.01
	3 courses	64.99±4.51*	63.54±3.16*	0.04	2.86	0.025	0.01
	4 courses	61.65±4.64*	59.48±4.99*	0.43	3.91	0.015	0.22
NO (μmol/L)	Pre-treatment	59.50±5.40	59.48±4.99	-1.86	1.90	0.586	0.002
	1 course	59.41±5.36	59.16±5.04	-1.63	2.13	0.290	0.02
	2 courses	68.38±7.49*	70.69±7.53*	-5.02	0.40	0.125	-0.15
	3 courses	81.43±7.64*	80.34±7.40*	-1.64	3.80	0.254	0.07
	4 courses	92.95±10.84*	97.25±6.99*	-7.61	-1.00	0.021	-0.23

Note: *P<0.05 vs pre-treatment; ET-1: Endothelin-1; NO: nitric oxide

It is suggested that both amlodipine alone and EECP combined with amlodipine has advantages in improving peripheral vascular resistance and EECP combined with amlodipine is better.

Comparison of FMD between the two groups

As can be seen in table 5, after 3 courses of treatment, there was no significant change in FMD in the combined group relative to the amlodipine group (P=0.169; P=0.475; P=0.524) and after 4 courses of treatment, a significant elevation in FMD was observed in the combined group relative to the amlodipine group (P=0.034). It is suggested that compared to amlodipine alone, EECP combined with amlodipine has advantages in improving vascular endothelialization in patients.

Comparison of WSS between the two groups

As can be seen in table 6, after 3 courses of treatment, compared to the amlodipine group, the combined group patients' WSS did not change significantly (P=0.109; P=0.112; P=0.524) and in the 4th course, after treatment, a significant increase in WSS was noted in the combined group versus the amlodipine group (P=0.035). It suggests that only amlodipine and amlodipine combined with EECP has advantages in increasing the avoidance of shear stress in patients' blood flow and that amlodipine combined with EECP is more effective.

Comparison of CFR between the two groups

From Table 7, after the first 3 courses of treatment, there was no significant difference in CFR levels (P=0.352; P=0.356; P=0.130) compared the combined group with the

amlodipine group. After the 4th course of treatment, both combined groups were higher relative to the amlodipine group (*P*=0.036). It is suggested that EECP combined with amlodipine has advantages in improving coronary blood flow.

Incidence of adverse reactions during treatment in the two groups

As can be seen in table 8, three patients in the amlodipine group experienced tachycardia, five nausea and vomiting and four dizziness and headache, with an incidence of adverse reactions of 20%, while one nausea and vomiting and two dizziness and headache occurred in the combined group, with an incidence of adverse reactions of 5%, suggesting that with the use of EECP in combination with amlodipine treatment, the patients' adverse reaction incidence rate was more lower (*P*=0.013).

DISCUSSION

As an independent risk factor for cardiovascular events in elderly patients with ISH, wide PP poses greater hazards than elevated SBP itself. Currently, drug therapy remains the cornerstone for the management of elderly ISH; however, monotherapy often fails to simultaneously achieve the dual goals of SBP control and PP improvement. In recent years, the clinical value of EECP has been confirmed in the treatment of cardiovascular diseases such as coronary heart disease (CHD) and heart failure. Nevertheless, the efficacy and mechanism of EECP combined with antihypertensive drugs in elderly ISH patients with wide PP have not been fully elucidated. (Rayegani *et al*., 2021). Based on this, this study focuses on hemodynamic parameters and vascular endothelial function indicators, comparing the therapeutic effects between EECP combined with amlodipine and amlodipine monotherapy. It aims to provide clinical evidence for optimizing the treatment regimen in elderly ISH patients with wide PP.

Blood pressure control constitutes the core goal in hypertension management. In this study, SBP was reduced from baseline in both patient groups after treatment, while the combined treatment group exhibited superior control efficacy. Specific data revealed that the SBP of the control group was 132.80±8.11 mmHg post-treatment, whereas that of the combined treatment group decreased to 128.53±6.62 mmHg. The inter-group difference was statistically significant (P=0.002), with a mean difference of 4.27 mmHg. Although this difference does not exceed the conventional clinical threshold for achieving target blood pressure reduction, its clinical significance cannot be overlooked when combined with the pathological characteristics of elderly patients with ISH. Elderly patients typically present with poor vascular elasticity; for every 2 mmHg reduction in SBP, the risk of stroke can be decreased by 10% and the risk of myocardial infarction by 7%. Based on this, it can be inferred that the combined treatment may further reduce the risk of cardiovascular events in patients by 14%-21% (Biswas *et al*., 2025). The improvement of PP stands out as a prominent highlight of this study. After treatment, the PP in the control group was 53.32±6.22 mmHg, while that in the combined treatment group decreased to 50.88±6.87 mmHg (P=0.044). Essentially, the improvement of PP reflects the enhancement of arterial elasticity. When arterial elasticity increases, the vasodilation capacity of blood vessels during cardiac systole is strengthened, leading to a reduction in the peak systolic blood pressure. Meanwhile, the elastic recoil capacity of blood vessels during diastole is improved, which mitigates the decreased amplitude of diastolic blood pressure. Consequently, the narrowing of PP is achieved. (Chen *et al*., 2023). As a key indicator reflecting the perfusion of tissues and organs, the MAP in the combined treatment group (94.61±7.21 mmHg) was significantly lower than that in the control group (97.26±6.37 mmHg) (P=0.035). This finding suggests that the combined treatment can maintain stable tissue perfusion while reducing blood pressure, thereby avoiding the risks associated with excessive blood pressure reduction. (Wu *et al*., 2025). Changes in SVR further reveal the mechanism of action of the combined treatment. After treatment, the SVR in the control group was 1567.73±170.41 dyn·s·cm^{-5}, while that in the combined treatment group decreased to 1494.95±143.75 dyn·s·cm^{-5} (P=0.013). The reduction in SVR indicates a significant decrease in peripheral vascular resistance, which is closely associated with the direct vasodilatory effect of amlodipine and the indirect vascular regulatory effect of EECP. The decrease in SVR not only reduces the afterload on the heart but also improves the blood perfusion of peripheral tissues, forming a positive cycle of blood pressure reduction, afterload alleviation and perfusion promotion (Yin *et al*., 2023, Zhang *et al*., 2024). Vascular endothelial dysfunction serves as the initiating factor in the occurrence and progression of wide PP in elderly patients with ISH. As core biomarkers of endothelial function, ET-1 and NO maintain a balanced state that directly reflects the integrity of endothelial function. ET-1 is a potent vasoconstrictor, while NO acts as the primary vasodilator; an imbalance between the two exacerbates vascular spasm and increases vascular stiffness. In this study, the ET-1 level in the combined treatment group after treatment was 59.48±4.99 pg/mL, which was significantly lower than that in the control group (61.65±4.64 pg/mL, P=0.015). In contrast, the NO level in the combined treatment group was 97.25±6.99 μmol/L, significantly higher than that in the control group (92.95±10.84 μmol/L, P=0.011). This change indicates that the combined treatment can effectively repair damaged vascular endothelial cells and restore the balance between ET-1 and NO, thereby improving vascular function at the pathophysiological root (Wang *et al*., 2023). As the gold standard for evaluating endothelial-dependent vasodilation function, the value of FMD directly reflects the responsiveness of blood vessels to blood flow stimulation.

Table 3: Comparison of SBP, PP and MAP ($\bar{x}\pm s$)

Indicator	Time	Mean ±SD		95% CI		*P*	Effect size
		Amlodipine group (n=60)	Combined group(n=60)	Lower	Upper		
SBP (mmHg)	Pre-treatment	170.70±6.84	172.72±7.82	-4.67	0.64	0.135	-0.14
	1 course	142.80±8.79*	144.03±7.48*	-4.18	1.72	0.253	-0.08
	2 courses	144.71±12.12*	143.52±8.69*	-2.62	5.02	0.221	0.06
	3 courses	137.53±9.16*	132.65±9.94*	1.43	8.34	0.015	0.25
	4 courses	132.80±8.11*	128.53±6.62*	1.59	6.94	0.022	0.28
PP (mmHg)	Pre-treatment	90.05±6.95	91.37±7.46	-2.92	1.29	0.219	-0.09
	1 course	62.48±4.46*	61.10±5*	-0.33	3.10	0.105	0.14
	2 courses	61.90±7.36*	60.28±4.99*	-0.66	3.89	0.124	0.13
	3 courses	58.08±4.55*	56.53±3.96*	0.01	3.09	0.035	0.18
	4 courses	53.32±6.22*	50.88±6.87*	1.20	0.07	0.041	0.18
MAP (mmHg)	Pre-treatment	110.67±5.76	111.81±5.56	-3.18	0.90	0.172	-0.10
	1 course	101.14±6.98*	103.3±5.52*	-4.43	0.12	0.095	-0.17
	2 courses	103.45±10.10*	103.33±7.86*	-3.15	3.39	0.541	0.007
	3 courses	98.81±10.04*	94.96±10.15*	0.20	7.50	0.041	0.19
	4 courses	97.26±6.37*	94.61±7.21*	0.19	5.10	0.040	0.19

Note: *P<0.05 vs pre-treatment; SBP: systolic blood pressure; PP: pulse pressure difference; MAP: mean arterial blood pressure

Table 4: Comparison of SVR between the two groups ($\bar{x}\pm s$, dyn-s-cm^{-5})

Indicator	Time	Mean ±SD		95% CI		*P*	Effect size
		Amlodipine group (n=60)	Combined group (n=60)	Lower	Upper		
SVR	Pre-treatment	2008.04±157.71	1987.46±186.68	-41.89	83.06	0.425	0.06
	1 course	1898.54±112.33*	1908.80±99.10*	-48.56	28.03	0.287	-0.05
	2 courses	1741.78±252.17*	1769.52±222.15*	-113.65	58.18	0.214	-0.06
	3 courses	1691.13±218.45*	1697.81±222.48*	-86.38	73.04	0.285	-0.02
	4 courses	1567.73±170.41*	1494.95±143.75*	15.79	129.78	0.023	-0.37

Note: *P<0.05 vs pre-treatment; SVR: peripheral vascular resistance

Table 5: Comparison of FMD between the two groups ($\bar{x}\pm s$, %)

Indicator	Time	Mean ±SD		95% CI		*P*	Effect size
		Amlodipine group (n=60)	Combined group (n=60)	Lower	Upper		
FMD	Pre-treatment	7.03±0.31	7.04±0.29	-0.12	0.09	0.528	-0.02
	1 course	7.61±0.67*	7.47±0.71*	-0.11	0.39	0.169	0.10
	2 courses	8.30±0.94*	8.25±0.89*	-0.28	0.38	0.475	0.03
	3 courses	9.00±0.63*	8.83±0.59*	-0.04	0.40	0.524	0.14
	4 courses	9.12±0.61*	9.42±0.81*	-0.56	-0.04	0.034	-0.20

Note: *P<0.05 vs pre-treatment; FMD: flow-mediated vasodilation

Table 6: Comparison of WSS between the two groups ($\bar{x}\pm s$, Pa)

Indicator	Time	Mean ±SD		95% CI		*P*	Effect size
		Amlodipine group (n=60)	Combined group (n=60)	Lower	Upper		
WSS	Pre-treatment	0.99±0.24	0.90±0.28	-0.01	0.18	0.125	0.17
	1 course	0.97±0.24	0.90±0.28	-0.02	0.16	0.109	0.13
	2 courses	1.56±0.45*	1.44±0.44*	-0.04	0.28	0.112	0.13
	3 courses	2.08±0.61*	2.06±0.66*	-0.20	0.26	0.524	0.02
	4 courses	2.52±0.34*	2.65±0.31*	-0.25	-0.01	0.035	-0.20

Note: *P<0.05 vs pre-treatment; WSS: wall shear stress

Table 7: Comparison of CFR between the two groups ($\bar{x}\pm s$)

Indicator	Time	Mean ±SD		95% CI		*P*	Effect size
		Amlodipine group (n=60)	Combined group (n=60)	Lower	Upper		
CFR	Pre-treatment	1.56±0.45	1.44±0.44	-0.04	0.28	0.142	0.13
	1 course	1.67±0.34	1.70±0.40	-0.16	0.11	0.352	-0.04
	2 courses	1.95±0.65*	2.06±0.66*	-0.34	0.13	0.356	-0.08
	3 courses	2.20±0.55*	2.24±0.55*	-0.25	0.15	0.130	-0.04
	4 courses	2.52±0.34*	2.65±0.31*	-0.25	-0.01	0.036	-0.20

Note: *P<0.05 vs pre-treatment; CFR: coronary flow reserve

Table 8: Comparison of the incidence of adverse reactions during treatment between the two groups of patients [n (%)].

Indicator	[n (%)]		95% CI		*P*	Effect size
	Amlodipine group	Combined group	Lower	Upper		
Tachycardia	3	0	1.266	17.819	0.013	0.227
Nausea and vomiting	5	1				
Dizziness and headache	4	2				
Adverse reactions	12 (20%)	3 (5%)				

After treatment, the FMD of the control group was 9.12±0.61%, while that of the combined treatment group increased to 9.42±0.81% (P=0.024). Although the magnitude of this increase is not significant, it holds clear clinical significance—for every 1% increase in FMD, the risk of cardiovascular events in hypertensive patients decreases by 12% (Yin *et al*., 2023). WSS refers to the tangential force exerted by blood flow on the vascular wall. An abnormal decrease in WSS can lead to vascular endothelial cell dysfunction. The WSS in the combined treatment group (2.65±0.31 Pa) was significantly higher than that in the control group (2.52±0.34 Pa) (P=0.030). This finding suggests that the combined treatment enhances the shear stimulation of blood flow on the vascular wall by improving hemodynamics, thereby promoting the repair and functional recovery of endothelial cells (Wu *et al*., 2023). As a key indicator for evaluating coronary reserve function, a decreased value of CFR indicates impaired diastolic reserve capacity of the coronary vascular bed, which serves as an early manifestation of CHD. In this study, the CFR of the combined treatment group was 2.65±0.31, higher than that of the control group (2.52±0.34, P=0.030). This result suggests that the sequential compression effect of EECP not only improves peripheral circulation but also enhances coronary reserve function by increasing coronary diastolic perfusion, thereby providing a protective effect against the development of CHD in elderly patients (Li *et al*., 2024). Treatment safety is a crucial consideration in the selection of therapeutic regimens for elderly patients. In this study, the incidence of adverse reactions in the combined treatment group was only 5%, which was significantly lower than the 20% in the control group (P=0.013). This result indicates that the combined use of EECP and amlodipine not only does not increase the risk of adverse drug reactions, but may also alleviate the side effects caused by amlodipine by improving peripheral circulation, thereby providing a favorable safety guarantee for the long-term treatment of elderly patients. (Duan and Tang, 2023).

From a comprehensive perspective, amlodipine reduces peripheral resistance by inhibiting L-type calcium channels in vascular smooth muscle, but fails to improve vascular stiffness in the elderly. EECP inflates the lower limb airbags during diastole, which promotes venous blood return, thereby increasing aortic diastolic blood pressure and coronary perfusion. During systole, deflation of the airbags reduces lower limb resistance and cardiac afterload, directly lowering SBP (Lin *et al*., 2023). Meanwhile, the diastolic stretching stimulation of EECP can promote the synthesis of elastin by vascular smooth muscle cells, narrowing PP. EECP increases blood flow velocity to enhance WSS, which activates endothelial shear stress receptors and promotes NO release, thereby forming a vasodilatory synergistic effect with amlodipine (Wang *et al*., 2023). In terms of endothelial repair, amlodipine reduces blood pressure to alleviate mechanical damage to the endothelium. EECP, on the other hand, increases perfusion to provide oxygen and nutrients required for endothelial repair, enhances WSS to activate the Akt/eNOS pathway and promote NO synthesis and simultaneously reduces oxidative stress damage. These effects collectively restore the balance between ET-1 and NO. The improvement in CFR is attributed to EECP increasing coronary perfusion pressure and NO-mediated coronary dilation, which synergizes with amlodipine to enhance coronary reserve function.

The results of this study are consistent with those of multiple previous studies, such as a systematic review that conducted a meta-analysis of 11 studies, which found that EECP can reduce patients' SBP. (Biswas *et al*., 2025) . EECP clinical trials established a hemodynamic model and showed that EECP can decrease patients' MAP, consistent

with the findings of this study (Chen *et al*., 2023). A randomized controlled trial conducted a 4-week EECP treatment on 83 patients and the results showed that EECP can reduce the level of ET-1 and increase the level of NO in serum, thereby improving vascular endothelial cell function and lowering blood pressure (Wang *et al*., 2023). A meta-analysis of 19 studies involving 1,647 patients confirmed that EECP can increase FMD (Yin *et al*., 2023).

The necessity of this study lies in the dual predicament encountered in the treatment of wide PP in elderly patients with ISH, monotherapy barely achieves both SBP control and PP improvement and there is a lack of effective interventions for endothelial injury. Existing combination medication regimens focus on blood pressure reduction, yet exert limited effects on improving vascular elasticity. Moreover, most studies on EECP have concentrated on patients with comorbid CHD, resulting in insufficient evidence for its application in isolated ISH with wide PP. Therefore, this study, which clarifies the value of EECP combined with amlodipine, is of great significance for solving clinical dilemmas. This study boasts three innovations. Firstly, it breaks through the limitation of focusing solely on blood pressure, taking hemodynamic indicators (such as SVR and CFR) and endothelial function indicators (such as ET-1 and FMD as the core to reveal the advantages of the combined therapy from the mechanism perspective. Secondly, it precisely focuses on the subpopulation of elderly patients with ISH and wide PP, avoiding confusion with general hypertension. Thirdly, it comprehensively evaluates the efficacy and safety of the combined therapy and clarifies the role of EECP in improving drug-related adverse reactions.

This study has several limitations. Retrospective non-randomized grouping is prone to selection bias, as patients with severe conditions or drug intolerance may be more inclined to receive combined treatment. Although there were no statistically significant differences in baseline characteristics, confounding factors cannot be completely excluded. Elderly patients often have comorbidities such as diabetes and hyperlipidemia and take multiple medications. This study did not conduct stratified analysis to explore the impacts of these factors, nor did it collect data on lifestyle factors such as smoking and exercise, making it difficult to control related confounders. The measurement of FMD is affected by the physician's experience, equipment and patient cooperation; the detection of ET-1 and NO is interfered by sample processing factors; CFR is calculated indirectly based on ultrasound and its accuracy is lower than that of invasive examinations. All these factors may lead to measurement errors (Liang *et al*., 2024). In addition, the sample size of 120 cases from a single center is limited and the patients are mainly those with normal BMI. Thus, the results cannot be directly generalized to obese patients or those from different regions. The EECP protocol was fixed in this study and the efficacy of different parameters needs further exploration. The observation period of four treatment courses only evaluated the short-term effects. Elderly patients with ISH require long-term management, so the long-term blood pressure-lowering effect of combined treatment, its role in preventing cardiovascular events and the safety of long-term EECP use all need to be clarified through extended follow-up. Moreover, the impact of long-term patient compliance on therapeutic efficacy also deserves attention. The analysis of adverse reactions was too superficial and no detailed risk-benefit interpretation was conducted, which limits its value in clinical guidance. In the future, prospective randomized controlled studies are needed to clarify the long-term efficacy and impact on cardiovascular endpoints. It is also necessary to explore optimized EECP parameter protocols to achieve personalized treatment, conduct in-depth research on molecular mechanisms and carry out subgroup analyses targeting special populations such as those with comorbid diabetes to expand the application scope of the treatment regimen. Additionally, risk-benefit analysis of adverse reactions should be performed to improve the clinical application value, thereby contributing to the prevention and control of cardiovascular diseases in the elderly.

CONCLUSION

The combination of EECP and amlodipine demonstrates superior efficacy and controllable risks in the treatment of elderly patients with ISH complicated by wide PP. This combined regimen provides a safe and optimized option for clinical practice and also offers important evidence for the precise treatment of elderly hypertension and subsequent research. In the future, large-sample randomized prospective studies are still needed to verify the conclusions of this study.

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Authors' contributions
Meili Ding: Conceived and designed the research and analyzed data. Drafted and revised the manuscript critically for important intellectual content; Jun Zhang and Zuliang Li: Contributed to the acquisition, analysis and interpretation of data. Provided substantial intellectual input during the drafting and revision of the manuscript; Jianqiao Yang: Participated in the conception and design of the study. Played a key role in data interpretation and manuscript preparation. All authors have read and approved the final version of the manuscript.

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Data availability statement
All data generated or analysed during this study are included in this published article.

Ethical approval
The clinical study followed the Declaration of Helsinki and other relevant ethical regulations and was reviewed and approved by Hangzhou Gongshu District People's Hospital of Integrated Traditional Chinese and Western Medicine Ethics Committee. (Ethics approval number: ZXY2021002). This study was performed in adherence with the STROBE guidelines. See supplementary file for the STROBE checklist.

Conflict of interest
The authors declare no conflicts of interest.

Consent to participate
We obtained written informed consent from every participant.

Supplementary data
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