

Efficacy of Antihypertensive Drugs of Diverse Categories after Unilateral Adrenal Chemical Ablation in Spontaneously Hypertensive Rats

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Abstract

Background

Unilateral adrenal chemical ablation (Ablation) effectively reduces blood pressure (BP) in spontaneously hypertensive rats (SHRs) with uncontrolled hypertension. However, few studies exist on the efficacy of diverse guideline-recommended antihypertensive drugs for the management of BP and target organ injury after ablation.

Methods

The BP values of SHRs that underwent ablation or sham operation were continuously monitored. Two weeks after surgery, SHRs were randomized to receive no antihypertensive medication, enalapril, sacubitril/valsartan (Sac/val), bisoprolol, amlodipine, or hydrochlorothiazide (HCT) for 4 weeks. BP and the remodelling of target organs, especially the heart and kidney, were explored.

Results

Before the administration of antihypertensive drugs, ablation effectively lowered BP in SHRs. At the end of the experiment, BP was lower in the ablation group than in the sham operation group in the drug-naïve control, enalapril, Sac/val, bisoprolol, amlodipine, and HCT groups. Among them, the largest BP changes were in the Sac/val and amlodipine groups. In drug-naïve controls, ablation also significantly reduced the plasma levels of renin, angiotensin II (Ang II), aldosterone, cortisol, norepinephrine, and epinephrine. Ablation followed by enalapril or Sac/val treatment further decreased the levels of aldosterone. A similar reduction in Ang II was shown only in the ablation group, which received the enalapril intervention. In the heart, ablation attenuated cardiac remodelling and function in SHRs, which was further improved by treatment with enalapril, bisoprolol, or Sac/val. In the kidney, ablation attenuated renal remodelling in SHRs, which was further ameliorated by treatment with enalapril, amlodipine or Sac/val. Among them, ablation followed by amlodipine further decreased the levels of urea nitrogen and creatinine.

Conclusions

After ablation, treatment with Sac/val or amlodipine led to the greatest reduction in BP. Ablation followed by antihypertensive medications plays a vital role in modulating renin–angiotensin–aldosterone system activity and cardiac and renal remodelling.

Introduction

Hypertension is a major contributor to the global disease burden, affecting over 1 billion adults worldwide, with its prevalence significantly increasing annually(1). Patients with hypertension face a

markedly increased risk of cardiovascular diseases, making cardiovascular disease one of the leading causes of premature death(2). Beyond its pressor effects, aldosterone excess directly promotes cardiovascular remodeling and fibrosis, establishing a direct path to heart failure and fatal arrhythmias (3, 4). Concomitantly, a hyperadrenergic state perpetuates hypertension by simultaneously constricting resistance vessels, potentiating central sympathetic outflow, dysregulating renin-angiotensin-aldosterone system (RAAS), and disrupting endothelial nitric oxide bioavailability-a confluence of mechanisms that accelerates target-organ damage(5–7). Therefore, as the primary organ responsible for aldosterone and catecholamine secretion, the adrenal gland represents a promising therapeutic target for future interventions in patients with hypertension.

Adrenal ablation, a minimally invasive catheter-based procedure that induces partial adrenal necrosis to suppress excessive hypertensive hormone secretion (8). Preclinical and clinical studies have demonstrated that adrenal ablation is a safe and effective treatment that significantly reduces the levels of adrenal-related hypertensive hormones (9–11). Our previous work demonstrated that unilateral adrenal chemical ablation with anhydrous ethanol significantly reduced blood pressure and serum levels of RAAS components and catecholamines in spontaneously hypertensive rats (SHRs), with improved target-organ remodeling in the heart, kidneys, and vasculature (12). These findings validate the safety and efficacy of unilateral adrenal chemical ablation for treating hypertension (13). Notably, while blood pressure remained lower than in sham-operated SHRs for six months post-procedure, a gradual rebound was observed starting from the second month, indicating that adjuvant antihypertensive therapy may be necessary to maintain long-term efficacy.

SHRs are a well-established and widely used animal model for hypertension research (14), and numerous studies have confirmed that they exhibit key pathophysiological features consistent with human adrenal-related hypertension (15–17). Specifically, SHRs spontaneously develop hypertension with increasing age, accompanied by abnormal activation of the renin-angiotensin-aldosterone system (RAAS)-a core pathophysiological mechanism of adrenal-related hypertension (18). These characteristics establish SHRs as a robust preclinical model for investigating adrenal-derived hypertensive hormones and their contribution to cardiovascular disease (19). For clinical practice, the primary goal of adrenal ablation is not to eliminate the need for antihypertensive medications but to improve blood pressure control, reduce drug burden, and minimize target-organ damage (20, 21). However, a critical clinical question remains: which class of guideline-recommended antihypertensive drugs (such as commonly used guideline-recommended medications, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor-neprilysin inhibitors (ARNIs), β -blockers, calcium channel blockers (CCBs), and diuretics) is most appropriate for patients following adrenal ablation to optimize blood pressure control and target-organ protection?

Therefore, this study focuses on SHRs as a research model and aims to investigate which class of guideline-recommended antihypertensive drugs can more effectively control blood pressure and protect target organs in SHRs undergoing adrenal chemical ablation. The goal of this study was to provide

theoretical evidence for the selection of antihypertensive medications for patients after adrenal ablation surgery in clinical practice.

Materials and methods

Animals

All animal experiments and protocols were approved by the Institutional Animal Care and Use Committee of Chengdu Medical College (CMC-IACUC-24-002). Eight-week-old male spontaneously hypertensive rats (SHRs) were purchased from Chengdu Dossy Experimental Animals Corporation (Chengdu, Sichuan, China) and housed in the pathogen-free animal facility of Chengdu Medical College under a 12-h/12-h light–dark cycle with free access to food and water.

After the experiments were completed, the rats were anesthetized by intraperitoneal injection of 2% sodium pentobarbital (40 mg/kg) in accordance with the AVMA guidelines for the euthanasia of animals, followed by euthanasia through intravenous injection of 2% sodium pentobarbital (200 mg/kg) via the tail vein. Under deep anaesthesia, blood samples were collected from the abdominal vena cava, after which the heart and kidneys were promptly excised.

Experimental protocols and groups of experiments

One hundred 12-week-old SHRs were randomized to undergo unilateral adrenal chemical ablation (Ablation) or a sham operation (Sham) using a computer-generated randomization sequence. Group allocation was performed by a researcher who was not involved in conducting the experiment or analyzing the data to avoid selection bias.

During the next two weeks (Phase I), all SHRs were maintained on a standard diet for environmental adaptation and postoperative recovery. No mortality or abnormal health conditions occurred during Phase I, and all 100 SHRs were included in Phase II without exclusions. In Phase II, the SHRs were further randomized to receive chow without antihypertensive drugs (control group) or chow with one of the following antihypertensive drugs via oral gavage. Each treatment and measurement were performed in random order to ensure consistency. The antihypertensive drugs and their dosages were as follows: (1) the angiotensin-converting enzyme inhibitor enalapril (Merck Sharp & Dohme, Australia; 20 mg/kg body weight/day) (22); (2) the angiotensin receptor–neprilysin inhibitor sacubitril/valsartan (Sac/val; Novartis Pharma Schweiz AG, Switzerland; 60 mg/kg body weight/day) (23); (3) the selective β 1-receptor blocker bisoprolol (Merck KGaA, Germany; 10 mg/kg body weight/day) (24); (4) the calcium channel blocker amlodipine (Pfizer Inc., America; 20 mg/kg body weight/day) (25); or (5) the thiazide diuretic hydrochlorothiazide (HCT; Yunpeng Pharmaceutical Group, China; 12.5 mg/kg body weight/day) (26). The antihypertensive drug dosage was selected based on the optimal concentration for reducing BP in SHRs, as reported in previous studies (17–21).

Outcome assessments and data analysis were conducted in a blinded manner to ensure unbiased results. In the study, n refers to the number of animals (detailed information as shown in each figure legend). Four rats did not survive to the end of the experiment and were excluded from the final data analysis.

Adrenal gland ablation

The rats were anaesthetized intraperitoneally with 2% sodium pentobarbital (40 mg/kg), and the hair on the back was removed using depilatory cream. After the skin was prepared, the rats were fixed on the experimental table. A 1–2 cm longitudinal incision was made along the midline of the back, approximately 1.5 cm caudal to the thoracic vertebrae, to expose the adrenal glands. A 0.5 ml syringe was used to inject 0.01 ml of either absolute ethanol or saline into the adrenal glands, as described in our previous study (12). After the procedure, the rats were placed in a recovery chamber. Penicillin (80,000 units/day) was administered for 3 days postoperatively to prevent infection.

Blood pressure measurement

BP in the rats was measured using a noninvasive tail-cuff system (Softron Biotechnology, Beijing, China). Prior to blood pressure data collection, rats underwent several training sessions involving restraint and blood pressure measurement. With repeated training, the animals became habituated to the procedure and exhibited rapid stabilization during measurements. The rats were placed on the measurement platform, and the tail cuff was gently fitted around the tail. The system was gradually heated to 39°C. Once the signal collection stabilized, the cuff was inflated to apply pressure until the pulse signal became a straight line. The cuff was then gradually deflated until a regular waveform signal appeared. At this point, the computer displayed the corresponding systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate values. Each rat was measured once every 3 minutes, with a total of 3 repetitions. The final values were calculated as the average of these three measurements (27). A six-week longitudinal blood pressure monitoring protocol was implemented post-ablation, with measurements taken at weekly intervals.

Biochemical measurements

Blood samples were collected from the subclavian veins of rats anaesthetized with 2% pentobarbital sodium and then centrifuged at $3000 \times g$ for 15 min to collect the serum. The levels of renin (#MM-0343R1), angiotensin II (#MM-0211R1), aldosterone (#MM-0555R1), cortisol (#MM-0574R1), epinephrine (#MM-0350R1), and norepinephrine (#MM-0556R1) were measured using commercial kits (Jiancheng Bioengineering, Nanjing, Jiangsu, China) following the manufacturer's instructions. The levels of serum potassium (#C013-2-1), serum sodium (#C013-2-1), urea nitrogen (#C013-2-1), and serum creatinine (#C013-2-1) were measured using a fully automated biochemical analyser (BS-420, Mindray, Shenzhen, China).

Histopathology

Histological analysis was conducted one month after adrenal ablation. Heart, kidney and adrenal gland samples were fixed, paraffin-embedded, and sectioned at a thickness of 4 μm . Heart sections were stained with haematoxylin and eosin (H&E), Masson's trichrome, and wheat germ agglutinin (WGA; green; Sigma-Aldrich) to evaluate histomorphology and interstitial fibrosis. Kidney sections were stained with H&E and Masson's trichrome; adrenal necrotic area was measured by H&E and Masson's trichrome to verify ablation efficacy.

Slides were examined using a microscope equipped with a digital camera (VS200, Olympus, Beijing, China) and analysed by Image-Pro Plus software version 7.0 (Media Cybernetics, Rockville, MD). Two observers blinded to groups analysed all slides (discrepancies resolved by senior pathologist). Quantitative metrics: (1) Cardiac: WGA staining for cardiomyocyte area (≥ 50 cells/section); Masson's staining for fibrosis ratio (5 fields/section). (2) Renal: GS score (28) (≥ 20 glomeruli/section); Masson's staining for renal fibrosis ratio (5 fields/section). (3) Adrenal: Necrotic area ratio (3–5 fields/section). Reproducibility was confirmed by duplicate analysis (ICC > 0.85).

Echocardiography

After 4 weeks of antihypertensive treatment, cardiac function in the rats was assessed using a small animal ultrasound system (EPIQ 7, Philips, Holland). In brief, the rats were anaesthetized and secured on the operating table. M-Mode imaging was used to obtain short-axis motion images of the heart, and measurements were taken for the left ventricular internal dimension in diastole (LVIDd) and interventricular septal diastolic thickness (IVSd). Indicators of left ventricular systolic function, such as the left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS), were calculated (29). These parameters were generally measured over 3 cardiac cycles, and the average values were recorded. The echocardiography procedures and subsequent data analysis were independently conducted by two technicians who were blinded to the study.

Statistical analysis

The results are expressed as the means $\pm$ SEMs. The experimental data were analysed using two-way analysis of variance (ANOVA) with multiple comparisons with GraphPad Prism 10 (GraphPad Software, La Jolla, CA, USA), and group comparisons were conducted using Tukey's *t* test. Pearson correlation analysis was used for correlation assessments, with statistical significance set at $P < 0.05$.

Results

Hypotensive effects of antihypertensive medication classes in addition to ablation

In phase I, no antihypertensive drugs were administered to any SHR. At the end of phase I, the MAP in the ablation group was significantly lower than that in the sham group (Fig. 1; $P < 0.01$). Similarly, the SBP (Figure S1A, $P < 0.01$) and DBP (Figure S2A; $P < 0.01$) in the ablation group were also obviously lower than those in the sham group. These results suggested that ablation was able to lower BP in SHRs.

With reference to our previous study (30), the adrenal ablation model was established and the area of adrenal necrosis was verified (Figure S3; $P < 0.01$). During phase II, the ablation and sham groups were randomly assigned to receive no antihypertensive drugs (drug-naïve control group), enalapril, Sac/val, bisoprolol, amlodipine, or HCT. At the end of phase II, MAP was significantly lower in SHRs that underwent ablation than in those that underwent sham exercise in the drug-naïve control group and the enalapril, Sac/val, bisoprolol, amlodipine, and HCT groups (Table 1; Fig. 1A-F; all $P < 0.01$). Moreover, SBP declined markedly in SHRs that previously underwent ablation compared with controls across the enalapril, Sac/val, bisoprolol, amlodipine, and HCT treatment groups (Table 1; Figure S1A-F; all $P < 0.01$). For DBP, a significant difference was observed between the sham and ablated animals in both the control and drug treatment groups (Table 1; Figure S2A-F; all $P < 0.01$).

Effects of ablation and antihypertensive medication classes on heart rate

To further investigate the effects of various types of antihypertensive drugs in SHRs subjected to ablation, the heart rate was measured. First, there was no significant difference in the baseline heart rate between the sham group and the ablation group. Furthermore, at the end of phase I, no obvious changes in heart rate were observed in SHRs or SHRs that received ablation (Fig. 2A-F; $P > 0.05$). In addition, the effects of various antihypertensive drugs on heart rate in the indicated groups were detected. Consequently, at the end of phase II, the heart rates were indistinguishable between ablation and sham surgery animals, regardless of the type of antihypertensive drug administered (Table 1; Fig. 2A-F; $P > 0.05$).

Effects of antihypertensive medication classes in addition to ablation on hormone levels

Overactivation of the renin–angiotensin–aldosterone system and sympathetic nervous system, which is mediated by hyperfunction of the adrenal gland, is strongly associated with hypertension (30). Therefore, the levels of hormones related to these systems in the indicated groups were measured. No statistically significant differences were observed in baseline hormonal parameters across groups before treatment initiation (Figure S4; $P > 0.05$). Compared with those in the sham-operated group, the plasma levels of renin, angiotensin II (Ang II), aldosterone, cortisol, norepinephrine, and epinephrine in the ablation group were significantly lower (Fig. 3; $P < 0.05$ or $P < 0.01$). Ablation followed by enalapril or Sac/val treatment further decreased the levels of aldosterone. For Ang II, only the ablation group that received the enalapril intervention exhibited an obvious reduction (Fig. 3B-C; $P < 0.05$ or $P < 0.01$). In addition, compared with

ablation, ablation followed by antihypertensive treatment had no effect on plasma renin, cortisol, norepinephrine or epinephrine levels (Fig. 3; $P > 0.05$).

Effects of antihypertensive medication classes in addition to ablation on cardiac function and remodelling

Histological analysis revealed that ablation attenuated the enlarged cardiomyocyte area and increased fibrosis in SHR, and these effects were further ameliorated by treatment with enalapril, bisoprolol, or Sac/val. Among those antihypertensive medications, Sac/val had the best effects ($P < 0.05$ or $P < 0.01$; Figs. 4A-C). Echocardiography demonstrated that ablation is able to rescue cardiac function in SHR, as evidenced by the reductions in IVSd and LVIDd and the elevations in LVFS and LVEF. Furthermore, ablation followed by enalapril, bisoprolol, or Sac/val further improved cardiac function ($P < 0.05$ or $P < 0.01$; Fig. 4D-H).

Effects of antihypertensive medication classes in addition to ablation on renal function and morphology

Ablation attenuated renal segmental sclerosis, reduced GS scores, and decreased renal fibrosis in SHR, which were further ameliorated by treatment with enalapril, amlodipine and Sac/val. Similarly, among the antihypertensive drugs, treatment with Sac/val resulted in greater improvement than treatment with enalapril or amlodipine ($P < 0.05$ or $P < 0.01$; Figs. 5A-D). With respect to biochemical indicators, ablation restored blood potassium levels while decreasing blood urea nitrogen and creatinine levels, with no effect on blood sodium levels in SHR ($P < 0.01$; Figs. 5E-H). Ablation followed by amlodipine further decreased the levels of urea nitrogen and creatinine ($P < 0.05$; Fig. 5G, H).

Discussion

Our previous research demonstrated that unilateral adrenal chemical ablation in SHR did not reduce blood pressure to normotensive levels. Hence, for unilateral adrenal chemical ablation treatment of hypertension, the primary goal is not to eliminate the need for postoperative medication but rather to better control blood pressure and reduce the burden of antihypertensive drugs, thereby minimizing the damage caused by hypertension to target organs. Therefore, most patients still require antihypertensive medications after surgery, but there is currently no clinical evidence to guide the selection of the most appropriate antihypertensive drug based on guideline recommendations. In this study, we investigated the effects of five guideline-recommended antihypertensive drugs, enalapril, sacubitril/valsartan, bisoprolol, amlodipine, and hydrochlorothiazide, on haemodynamics and hypertension-mediated target organ damage. Several novel observations were made in this study. First, unilateral adrenal chemical ablation combined with different classes of antihypertensive drugs could reduce the blood pressure of SHR, with the most significant changes observed with sacubitril/valsartan and amlodipine treatments. Second, unilateral adrenal chemical ablation, sacubitril/valsartan, and enalapril each suppressed RAAS

activity to varying degrees. Treatment with sacubitril/valsartan or enalapril following unilateral adrenal chemical ablation further reduced aldosterone levels. Third, unilateral adrenal chemical ablation combined with different classes of antihypertensive drugs improved target organ damage in the heart and kidneys of SHR to varying degrees.

Adrenal ablation is a safe and effective treatment for primary aldosteronism (PA)-related hypertension (31). Based on a comprehensive analysis of current studies related to adrenal ablation, the therapeutic efficacy of this method for treating PA is as follows: the complete blood pressure control rate ranges from approximately 12.9–25% (32), with a partial remission rate of 25.8–44% (9); the complete biochemical control rate is between 41.4% and 60% (33); and the partial remission rate ranges from 17.2–24% (34). Postoperatively, patients with PA exhibit significantly reduced aldosterone levels and a marked decrease in the defined daily dose of antihypertensive medications (35). Randomized controlled trials have demonstrated that 81% of patients with PA who underwent transcatheter adrenal ablation achieved complete or partial remission of hypertension and biochemical abnormalities. Compared with medical therapy, adrenal ablation is more effective in lowering aldosterone levels and reducing medication requirements (10). However, most patients still require continued oral antihypertensive treatment after surgery. There is no consensus in clinical practice regarding which antihypertensive drugs should be used for hypertension management in patients following adrenal ablation.

SHRs are important models for hypertension research, as their target organ pathological changes closely resemble those observed in human hypertension, making them valuable tools for studying hypertension and its related diseases (36). In adult SHRs, target organ damage is evident, with cardiac damage manifesting primarily as myocardial hypertrophy, cardiomyocyte apoptosis, and fibrosis (37–39). Renal damage is characterized by glomerulosclerosis and tubulointerstitial fibrosis (40, 41). Current evidence suggests that target organ damage in SHRs is related primarily to sustained hypertension, activation of the RAAS, and sympathetic nervous system activity (42). Compared with normotensive control Wistar-Kyoto rats, SHRs exhibit more active synthesis of hypertension-related hormones, such as aldosterone and catecholamines, resulting in higher plasma levels of these hormones (43). Nevertheless, given the inherent differences between preclinical models and clinical settings, particularly that SHRs cannot fully recapitulate the etiological heterogeneity of human adrenal-related hypertension, our findings should be extrapolated to humans with caution and further clinical trials are warranted to validate the efficacy of different antihypertensive drug classes in patients with adrenal-related hypertension after Ablation.

Ablation leads to the loss of function in part of the adrenal tissue, reducing the secretion of hypertension-related adrenal hormones such as aldosterone and catecholamines, thereby inhibiting the activation of the RAAS and decreasing sympathetic nervous system activity (44). However, previous studies have shown that blood pressure begins to rebound by the eighth week after unilateral adrenal chemical ablation, and target organ damage persists to varying degrees. This rebound hypertension and sustained target organ damage may be related to the activation of the RAAS and increased sympathetic nervous system activity in SHRs. In the present study, SHRs were randomized into ablation and sham

groups, with antihypertensive treatments initiated at two weeks postoperatively. We observed that ACEI treatment not only markedly reduced blood pressure, plasma aldosterone, and angiotensin II levels, but also further alleviated cardiac and renal remodeling. These beneficial effects likely reflect ACEI-mediated RAAS inhibition, which secondarily reduces sympathetic outflow, thereby enhancing blood pressure lowering and protecting against target organ damage after adrenal ablation (45). Notably, ARNIs demonstrated more pronounced reductions in blood pressure and aldosterone levels compared to ACEIs, while maintaining significant efficacy in attenuating cardiac and renal target organ damage. Mechanistically, ARNI exerts dual modulation by simultaneously inhibiting RAAS and enhancing the natriuretic peptide system, which promotes natriuresis, vasodilation, and suppression of maladaptive remodeling (46). When combined with adrenal ablation, ARNI acts via a complementary dual mechanism: ablation targets the adrenal source of hypertension-related hormones, whereas ARNI enhances natriuretic peptide signaling and blocks RAAS-mediated vasoconstriction and sodium retention. This synergistic interaction between adrenal ablation and ARNI therapy underlies the more robust and sustained blood pressure reduction and superior organ protection observed in this study.

Clinically, β_1 receptor blockers are generally not very effective at lowering blood pressure (47). However, in this study, we observed that in the bisoprolol group, the decrease in blood pressure in the unilateral adrenal chemical ablation group was significantly more pronounced, exceeding that in the sham surgery group by 27.5 mmHg. We hypothesize that unilateral adrenal chemical ablation reduces the secretion of adrenal-related hypertensive hormones, whereas bisoprolol effectively suppresses sympathetic nervous activity (48). The combined effects of surgery and medication complement each other, thereby enhancing the blood pressure-lowering effect. Therefore, for patients with suboptimal blood pressure control after adrenal ablation, β_1 receptor blockers may be a good therapeutic option. Further studies are warranted to clarify the precise mechanisms underlying this interaction.

CCBs are among the most effective antihypertensive agents. Although CCBs do not fully reverse cardiac remodeling, they block voltage-dependent calcium influx through L-type calcium channels, resulting in dilation of both afferent and efferent glomerular arterioles. This reduction in glomerular filtration pressure helps prevent renal arteriosclerosis, preserve renal function, and protect against the development of hypertensive nephropathy (49). When combined with ablation, CCBs act through distinct yet complementary pathways: ablation reduces hormone-dependent hypertensive stimuli, while CCBs directly induce vasorelaxation via calcium channel modulation. This mechanistic synergy explains the marked blood pressure-lowering efficacy of adrenal ablation combined with CCB therapy.

Our study demonstrated that enalapril, sacubitril/valsartan, amlodipine, and bisoprolol are all first-line drugs for hypertension that can effectively lower blood pressure in SHRs after unilateral adrenal chemical ablation while also improving target organ remodelling in the heart or kidneys. Based on the findings of this study, if blood pressure remains uncontrolled after unilateral adrenal chemical ablation, it may be reasonable to add ARNIs or CCBs. This finding is particularly important because most patients, although their blood pressure is controlled, still require pharmacological treatment.

Limitations

In our study, SHRs were treated with antihypertensive medications for only four weeks, which may have been too short a duration to assess the extent of improvement in target organ damage accurately. In clinical practice, some patients require two or more antihypertensive drugs after unilateral adrenal chemical ablation. This study did not explore the effects of combination therapy with multiple antihypertensive agents on SHRs following unilateral adrenal chemical ablation. The doses of the medications used in our study were based on previous research on SHRs. Among these, enalapril, sacubitril/valsartan, and amlodipine were the most effective in lowering blood pressure. However, we cannot exclude the possibility that the doses of antihypertensive drugs may have been too low or that the treatment duration was too short, which might have limited the full antihypertensive effects of the medications. Another potential limitation is that blood pressure was determined using tail-cuff plethysmography, which is less precise than radiotelemetry despite adequate animal training and standardized measurement conditions.

Abbreviations

BP Blood pressure

SHRs Spontaneously hypertensive rats

Sac/val Sacubitril/valsartan

HCT Hydrochlorothiazide

Ang II Angiotensin II

RAAS Renin-angiotensin-aldosterone system

ACEIs Angiotensin-converting enzyme inhibitors

ARNIs Angiotensin receptor-neprilysin inhibitors

CCBs Calcium channel blockers

SBP Systolic blood pressure

DBP Diastolic blood pressure

MAP Mean arterial pressure

H&E Haematoxylin and eosin

WGA Wheat germ agglutinin

LVIDd Left ventricular internal dimension in diastole

IVSd Interventricular septal diastolic thickness

LVEF Left ventricular ejection fraction

LVFS Left ventricular fractional shortening

ANOVA Analysis of variance

PA Primary aldosteronism

Declarations

Ethics approval and consent to participate

All experimental protocols were reviewed and approved by the Research and Ethics Committee of the Chengdu Medical College. All procedures conformed to internationally accepted guidelines and ethics for animal research. All authors confirm that all methods are reported in accordance with ARRIVE guidelines for the reporting of animal experiments. Great efforts were made to reduce the total number of animals used and to minimize their suffering.

Consent for publication

Not applicable.

Availability of data and materials

All datasets and materials will be available upon request to the corresponding author.

Competing Interests

No competing financial interests exist.

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Authors' contributions

Conceptualization, Tao Luo; Methodology, Qianwei Yang; Software, Jindong Wan; Validation, Xinquan Wang, Sen Liu and Dan Wang; Formal Analysis, Yaqiong Zhou and Jixin Hou; Investigation, Ruixue Duan; Resources, Yidan Wang; Data Curation, Yuhang Lv; Writing – Original Draft Preparation, Peijian Wang and Tao Luo; Writing – Review & Editing, Yi Yang and Qianwei Yang; Visualization, Yi Yang; Supervision, Qianwei Yang; Project Administration, Tao Luo and Qianwei Yang; Funding Acquisition, Peijian Wang and Yi Yang.

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Table 1

Table 1 is available in the Supplementary Files section.

Figures

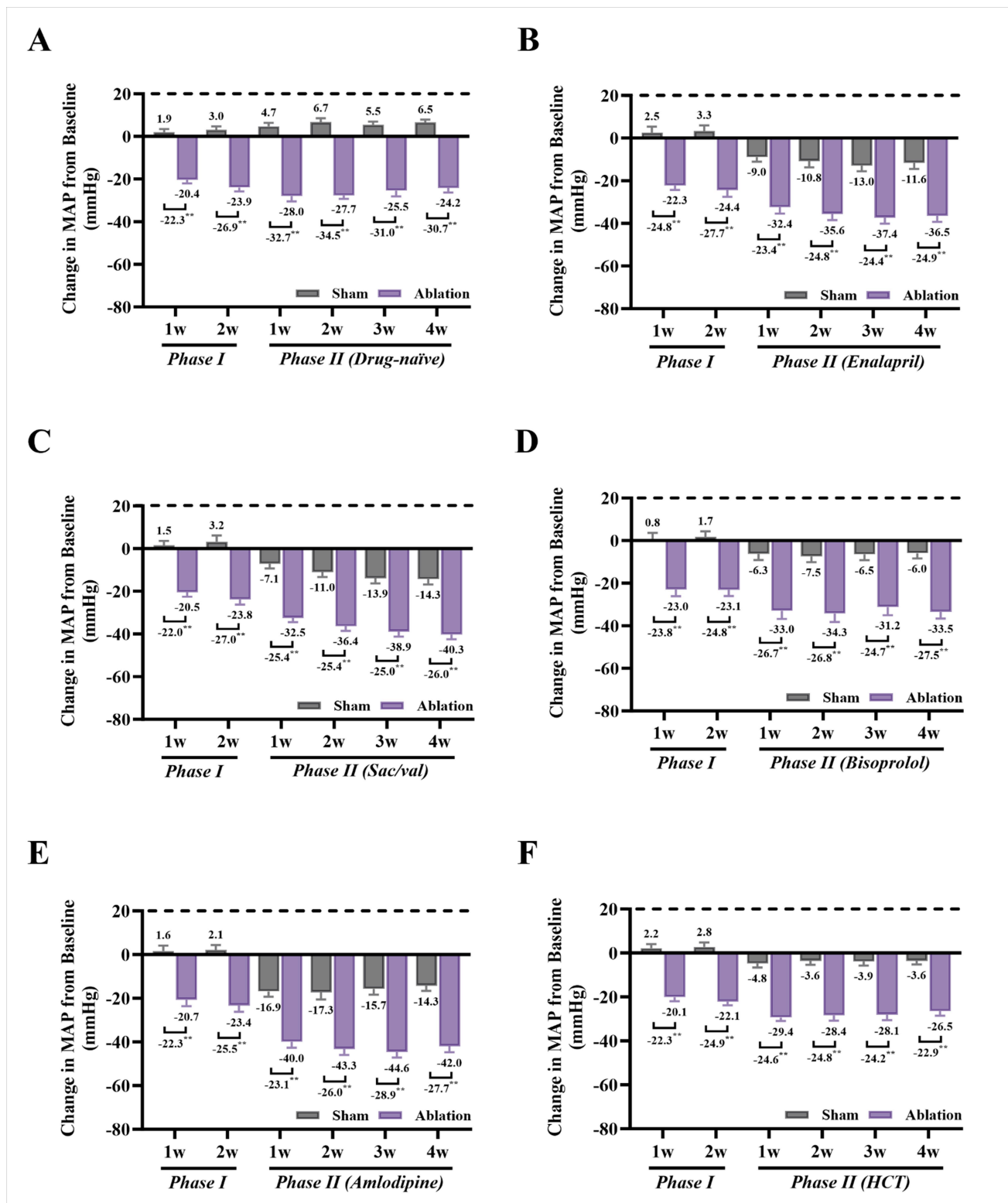


Figure 1

Effects of different classes of antihypertensive drugs on the MAP of SHRs after ablation or sham operation. MAP was measured in each group of SHRs at 2 and 4 weeks after drug intervention to evaluate the differences between the MAP and baseline mean arterial pressure at different experimental stages. MAP was measured continuously for six weeks post-ablation in SHRs without antihypertensive treatment (A) and in SHRs treated with enalapril (B), sacubitril/valsartan (C), bisoprolol (D), amlodipine

(E), or hydrochlorothiazide (F) Sac/val, sacubitril/valsartan; HCT, hydrochlorothiazide. The data are presented as the means $\pm$ SEMs (n=8 per group). ** $P<0.01$.

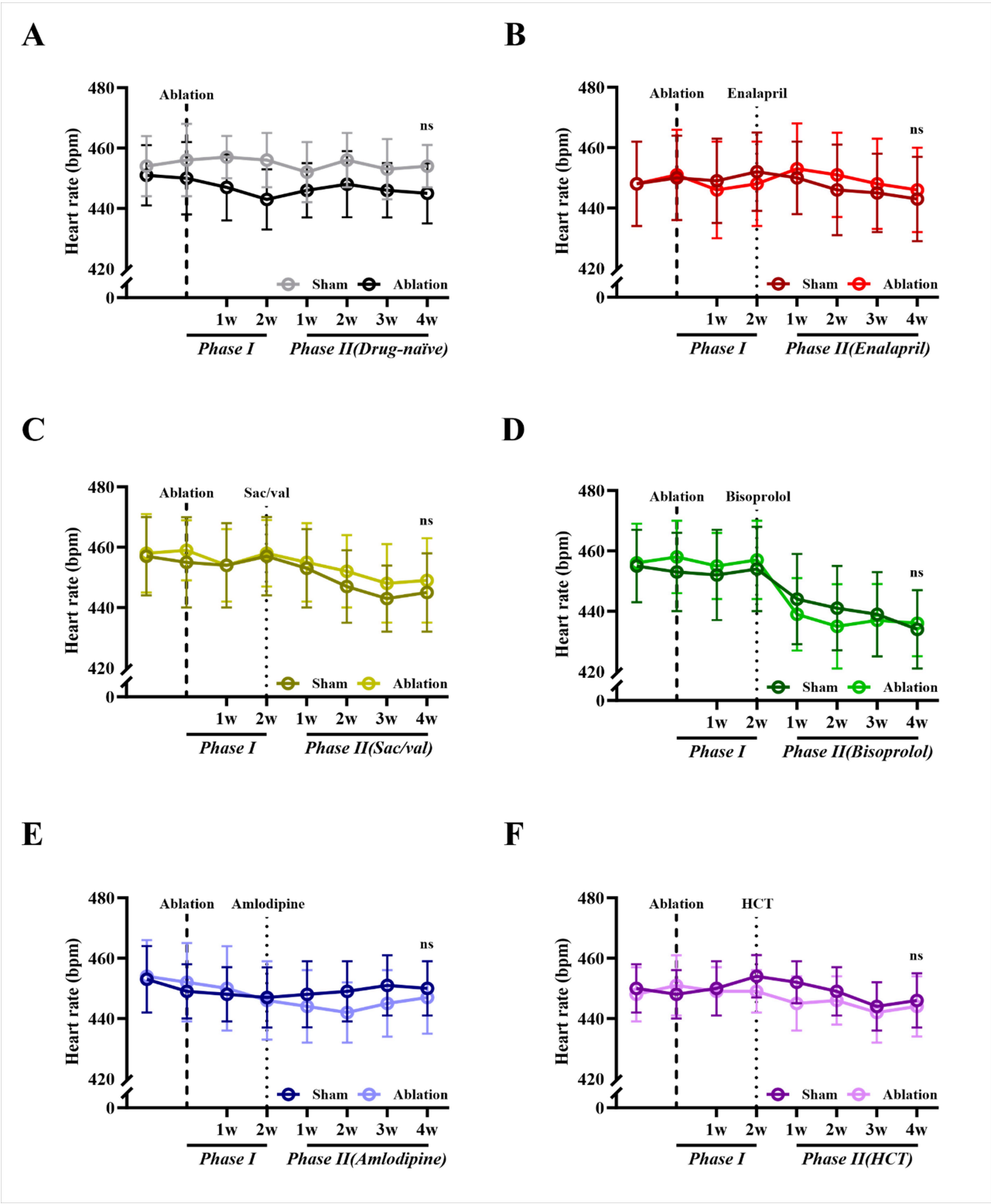


Figure 2
The effects of various types of antihypertensive drugs on heart rate after ablation. (A-F) Heart rate was assessed in SHRs treated with ablation or sham surgery, with and without antihypertensive drugs. Heart

rate was measured in SHRs without antihypertensive treatment (A) and in SHRs treated with enalapril (B), sacubitril/valsartan (C), bisoprolol (D), amlodipine (E), or hydrochlorothiazide (F). The data are presented as the means $\pm$ SEMs (n=8 per group). NS indicates no significance.

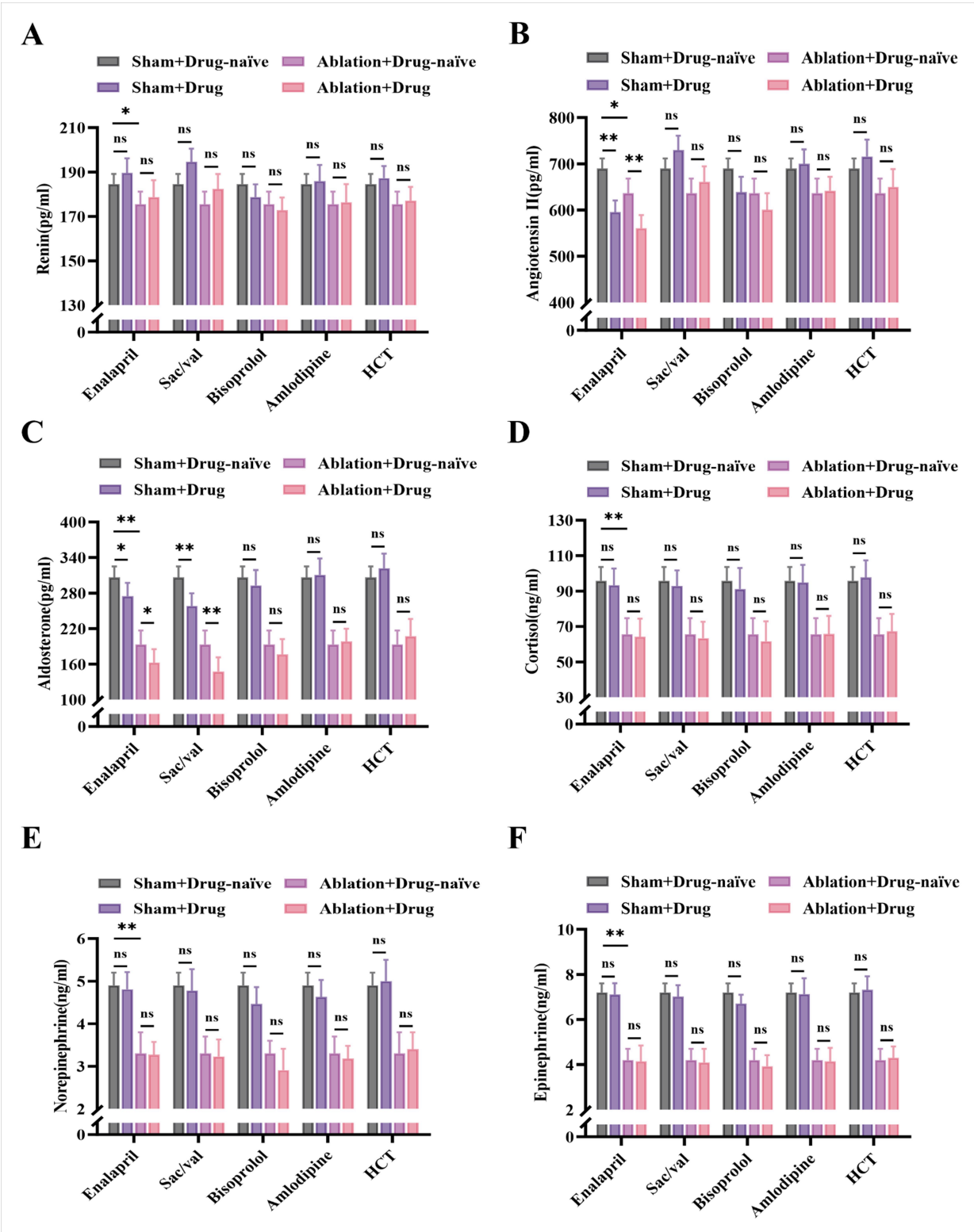


Figure 3

The effects of different classes of antihypertensive drugs on adrenal-related hormones treated with ablation. (A-F) Plasma levels of renin (A), angiotensin II (B), aldosterone (C), cortisol (D), norepinephrine (E), and epinephrine (F) were measured in SHRs receiving ablation or sham surgery across different drug treatment groups. The data are presented as the means $\pm$ SEMs (n=8 per group). * P <0.05; ** P <0.01; NS indicates no significance.

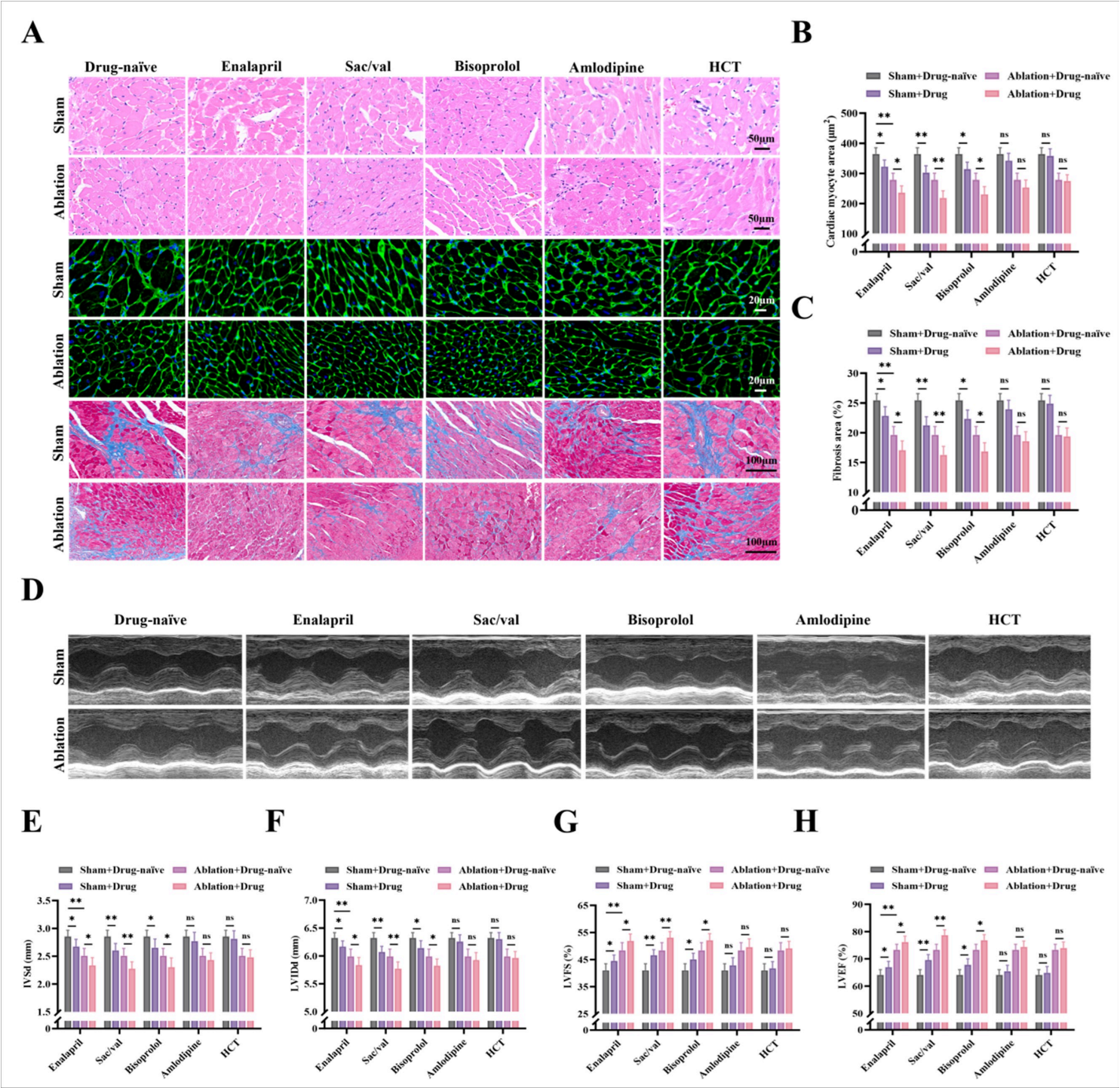


Figure 4

Effects of different treatments on the cardiac structure and function of SHR. (A) Representative images of wheat germ agglutinin staining, haematoxylin and eosin (H&E) staining, and Masson's trichrome staining in different treatment groups. (B) The average cardiomyocyte cross-sectional area was measured. (C) Quantitative analysis of the myocardial fibrosis area. (D) Representative echocardiographic images from each group. (E-H) Echocardiographic assessment of IVSd, LVIDd, LVFS and LVEF was used to assess cardiac function. The data are presented as the means $\pm$ SEMs (n=8 per group). * P <0.05; ** P <0.01; NS indicates no significance.

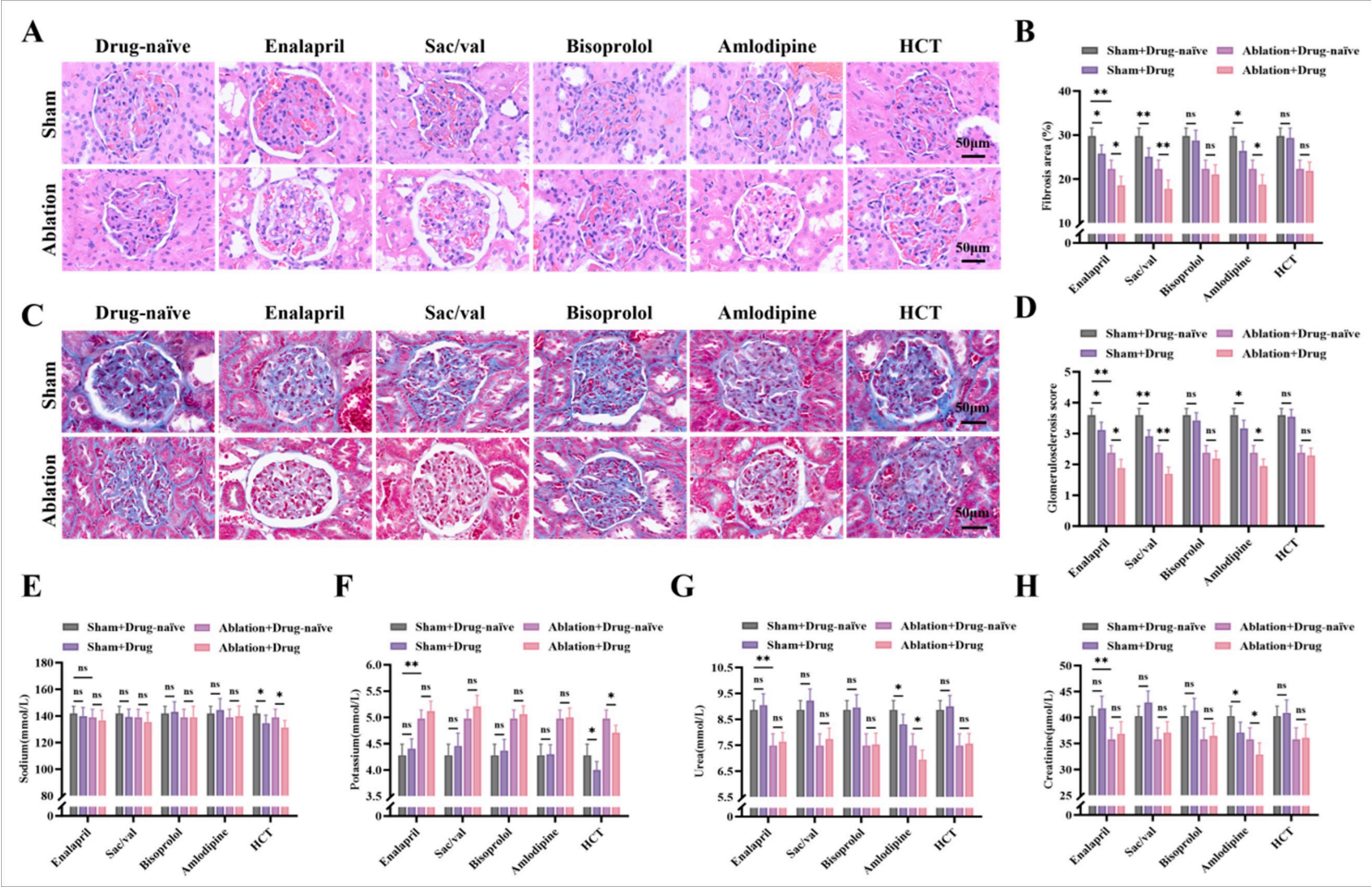


Figure 5

Effects of different treatments on renal structure and function. (A-B) Representative images of H&E-stained samples (A) and glomerulosclerosis scores (B) in the indicated groups. (C-D) Representative Masson's trichrome staining (C) and fibrotic areas were quantified in the different treatment groups. (E-H) Plasma levels of sodium (E), potassium (F), blood urea nitrogen (G), and creatinine (H) were measured across groups. The data are presented as the means $\pm$ SEMs (n=8 per group). * P <0.05; ** P <0.01; NS indicates no significance.

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