ORIGINAL ARTICLE

Effects of late-onset and long-term captopril and nifedipine treatment in aged spontaneously hypertensive rats: Echocardiographic studies

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The purpose of the present study was to analyze the changes in blood pressure, left ventricular (LV) wall thickness and LV systolic function of aged spontaneously hypertensive rats (SHRs) either with or without antihypertensive therapy. Twenty-one SHRs aged 60.5 ± 0.25 weeks were investigated over 22 weeks. They were divided into the following three groups (7 per group): untreated controls (CTRL), treatment with captopril (CAP, 60 mg kg⁻¹ daily) and treatment with captopril plus nifedipine (CAP+NIF, 60+10 mg kg⁻¹ daily). Systolic blood pressure (SBP) was regularly measured using the tail cuff method, and an echocardiogram was repeatedly obtained to examine the LV systolic and diastolic area, LV systolic fractional area change, cardiac output and LV myocardial wall thickness. Finally, heart catheterization was performed. While SBP remained stable in the CTRL animals over the experimental period, both of the antihypertensive treatments significantly reduced SBP by 20% in the treated animals ($P < 0.001$). Echocardiography demonstrated that both the systolic and the diastolic LV function of the untreated SHRs deteriorated over time, whereas both types of antihypertensive treatments attenuated and delayed but did not completely prevent the decline in LV systolic function. Cardiac output, as determined by pulsed wave Doppler echocardiography, remained significantly higher in the treated animals than in CTRLs until week 20, but it then decreased. Heart catheterization showed a significant decrease in LV function, as reflected by the LV systolic pressure and contractility, in the CTRLs but not in treated animals. These findings clearly indicate that late-onset antihypertensive treatment with CAP or CAP+NIF is beneficial with respect to blood pressure reduction, LV hypertrophy attenuation and LV systolic function preservation.

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INTRODUCTION

With a mortality rate of 40%, cardiovascular diseases such as myocardial infarction, stroke and heart failure are among the top causes of death in the European Union.¹ Although major progress has been made in the treatment of hypertension, there are serious problems concerning diagnosis and, consequently, the late onset of antihypertensive therapy.

Numerous studies on young spontaneously hypertensive rats (SHRs) have clearly documented that the effects of antihypertensive treatment on blood pressure and cardiovascular function significantly depend on the age at which therapy is started.^{2–5} An echocardiographic study showed that cardiac hypertrophy in SHRs starts to develop by as early as 4 weeks of age and results in significant systolic and diastolic dysfunction at 2–3 months of age.⁶ Transient treatment with captopril during this phase was found to prevent the development of cardiac and vascular remodeling.⁷

The aim of the present study was to analyze the long-term effects of hypertension and of antihypertensive treatment that is started late in life in aged SHRs. According to typical therapeutic regimens in humans, the effects of a monotherapy and a combination of two drugs should be examined. These treatments were chosen based on a preliminary systematic treatment study in 42 young SHRs treated with antagonists of calcium channels, the sympathetic nervous system and the renin-angiotensin system.⁸ These classes of drugs represent substantial principles of antihypertensive therapy. They act on essential mechanisms of hypertension and cardiac remodeling, thereby significantly reducing blood pressure and attenuating left ventricular (LV) remodeling.^{9–12} Specifically, we used the angiotensin-converting enzyme inhibitor captopril, the calcium channel antagonist nifedipine and the β -adrenergic antagonist propranolol as monotherapies and in various combinations. To treat the aged SHRs, we chose two therapies; one was captopril, and the other was a combination of captopril and

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nifedipine because these treatments have produced the best results for reducing SBP.⁸ In particular, captopril had repeatedly been shown to be effective in reducing blood pressure and in preventing cardiac hypertrophy and the deterioration of LV pump function in adult and elderly SHR.^{5,9}

Particular emphasis was directed to the repeated *in vivo* monitoring of blood pressure and cardiac function in SHR with and without therapy. Echocardiography was used to document the development of hypertension-induced cardiac changes, including LV myocardial hypertrophy and dysfunction. Aged SHR are an appropriate model for studying the transition from stable compensated hypertrophy to decompensated heart failure because their incidence of heart failure increases exponentially.¹³ The present study mainly focused on whether and to what extent late-onset antihypertensive therapy can attenuate cardiac hypertrophy, dilatation and LV dysfunction, and can delay or even prevent the transition to cardiac failure.

METHODS

Animals

Twenty-one male SHR (Charles River Laboratories, Sulzfeld, Germany) that were 60.5 ± 0.25 weeks of age and weighed 404 ± 31 g were enrolled in our

study. The animals were supplied by the institutional Animal Care Center, with breeding pairs originating from Charles River (Germany). The experiment was scheduled to last for 22 weeks. All of the animals were fed a standard pellet diet (Altromin C100, Altromin GmbH, Lage, Germany) and had free access to tap water. The experiments were approved by the state agency in accordance with the EU guidelines on animal use.

Experimental groups

The SHR were randomly divided into three groups either with or without antihypertensive treatment. The first group ($n=7$) received a placebo and served as hypertensive controls (CTRL, average body weight (BW) = 397 ± 10 g). The second group ($n=7$; 402 ± 18 g) was treated with the angiotensin-converting enzyme inhibitor captopril (CAP, 60 mg kg^{-1} per day, Axxora, Lörrach, Germany). The third group ($n=7$; 415 ± 9 g) received a combination therapy of CAP and the calcium antagonist nifedipine (CAP+NIF, $60+10 \text{ mg kg}^{-1}$ per day, Sigma, Sigma-Aldrich Chemie, Steinheim, Germany). These therapeutic regimens were chosen because they provided the best antihypertensive results in a preliminary systematic treatment study among young SHR.⁸ The drugs were added to commercially available rodent sweets (tablets) and administered daily *per os* between 9 and 10 a.m. During a preliminary 2-week period, the animals were accustomed both to the drug-free tablets and to the procedure of measuring their blood pressure.

Figure 1 Original echocardiographic recordings of the rat left ventricle (LV) from the short-axis parasternal view without (left side) and with (right side) LV dimensions. The areas within the circles represent the left ventricular systolic area (LV_syst) (a) and the left ventricular diastolic area (LV_diast) (b); in (c), the left ventricular myocardial area (LV_MA) is the area between the pericardial area (dashed line) and the diastolic area (solid line).

Blood pressure measurements

Systolic blood pressure (SBP) was determined using the tail cuff method (TSE series 209002, TSE Systems GmbH, Bad Homburg, Germany). The measurements were taken in experimental weeks 1, 2, 4, 6, 8, 11, 14, 17 and 20. In the treated animals, the procedure started 1 to 2 h after drug administration. The animals were placed on a heated plate (36 °C) and were held loosely on their back or tail by the experimenter's hand, which allowed them to move relatively freely. This method is less stressful than the use of a conventional restraint box, and it was tolerated much better by the animals. After six to eight preliminary tests, the animals became familiarized with the environment and procedure, and they remained quiet during the measurements. For each SBP measurement, the mean was calculated from two to three tests, each consisting of 10 single readings.

Echocardiographic measurements

Echocardiograms were performed by an experienced echocardiographer in experimental weeks 4, 8, 12, 16, 20 and 22 using a commercially available ultrasound system (GE Vivid 7 equipped with an 11.5 MHz sector scan probe, GE Healthcare Technologies Norway AS, Oslo, Norway). The dimensions and wall thickness of the LV chamber were measured using two-dimensional imaging in the parasternal short axis at the largest diameter of the LV. Aortic outflow was estimated using pulsed wave Doppler echocardiography in the sternal apical axis. The Doppler sample volume was positioned using two-dimensional guidance and verified by real-time auditory and visual display of the Doppler data at 200 mm s⁻¹. The animals were anesthetized using 2% isoflurane and examined in the left lateral decubitus position. The electrocardiogram was simultaneously recorded.

For the offline analysis of the echocardiographic data, we used the ultrasound analysis software EchoPac PC (GE Healthcare Technologies Norway AS). LV systolic function was assessed by determining the LV systolic area (LV_{syst}), LV systolic fractional area change (LV_{FAC}) and cardiac output (CO). For this assessment, the LV systolic and diastolic areas were measured when the systolic area was the smallest (LV_{syst}, Figure 1a) and when the diastolic area was the largest (LV_{diast}, Figure 1b), respectively. LV_{FAC} was estimated to be the difference between LV_{diast} and LV_{syst} as a percent of LV_{diast}. CO was calculated from the velocity-time integral of the aortic outflow (VTI), the LV outflow tract (LV_{OT}), and the heart rate (HR) according to the following equation: CO [ml min⁻¹] = VTI [cm] · LV_{OT} [cm²] · HR [min⁻¹]. Owing to physical limitations, an exact determination of the LV_{OT} could not be made; thus, a constant area of 0.071 cm² was assumed. The LV_{diast} served as an indicator of LV dilatation. Myocardial hypertrophy was determined by LV wall thickness, which was roughly assessed by the LV myocardial area (LV_{MA}). LV_{MA} was calculated as the difference between the pericardial area and the diastolic area of the LV cavity¹⁴ (Figure 1c).

Figure 2 Systolic blood pressure measured using the tail cuff method. Data are given as the mean $\pm$ s.e.m. CTRL, untreated SHR (n=5-7); CAP, treatment with captopril (n=6-7); CAP+NIF: treatment with captopril + nifedipine (n=7). Significance marks: □ CAP significant vs. time-matched CTRL ($P < 0.001$); ▲ CAP+NIF significant vs. time-matched CTRL ($P < 0.001$); † CAP significant vs. baseline (B; $P < 0.001$); ‡ CAP+NIF significant vs. baseline ($P < 0.001$).

Hemodynamic measurements

At the end of the experimental period (that is, after week 22), the animals were weighed and were anesthetized by i.p. injection of 80 mg kg⁻¹ thiopental sodium (Trapanal, Byk Gulden, Konstanz, Germany). They were tracheotomized, and a polyethylene cannula was placed in the trachea. The right ventricle and left ventricle (LV) were catheterized with Millar ultraminiature catheter pressure transducers (Millar Instruments, Houston, TX, USA), as previously described,^{15,16} to measure the right ventricle systolic pressure and the LV systolic pressure. In addition, right ventricle and LV contractility (dP/dt max) and relaxation (dP/dt min) were assessed. After the withdrawal of the LV catheter tip into the aorta, the diastolic aortic pressure was measured to calculate the mean aortic pressure. Finally, the animals were killed, and the heart was rapidly excised and weighed. The heart weight (HW) was normalized to the baseline BW (HW/BW), which served as a measure of cardiac hypertrophy.

Statistical analysis

The data are presented as the mean $\pm$ s.e.m. To evaluate the differences among the three groups, we used a multiple-sample comparison test and a *post hoc* multiple range test by applying the Bonferroni procedure (STATGRAPHICS; Statistical Graphics Corp., Rockville, MD, USA). Repeated measures analysis of variance was used to evaluate differences over time within each therapy group by SIGMAPLOT (Systat Software GmbH, Erkrath, Germany). Differences were considered significant if $P < 0.05$.

RESULTS

Three of the CTRL animals died prior to the final echocardiographic and hemodynamic measurements. The first one died after 8 experimental weeks, presenting with cachexia, dehydration and ileus symptoms. At necropsy, we found a tumor in the bowel. The second one died after 16 weeks with clinical and echocardiographic signs of severe pulmonary edema. The third one died after 20 weeks and presented with pleural effusion at necropsy. Only one of the rats that received antihypertensive treatment (CAP) died prematurely. This animal seemed extremely excited and died suddenly from cardiac arrest during the blood pressure measurement in experimental week 3. Necropsy did not reveal any pathological features.

Blood pressure

Baseline SBP was similar in all three groups (CTRL, 230 ± 9 mm Hg; CAP, 230 ± 13 mm Hg; and CAP+NIF, 245 ± 8 mm Hg). Though SBP in the untreated CTRL group remained stable over time (240 ± 5 mm Hg at week 20, $P = 0.07$), both types of antihypertensive therapy induced a significant reduction in SBP after a few weeks of treatment. At the final measurement (week 20), SBP was 185 ± 5 mm Hg (-19.6% vs. baseline, $P < 0.001$) in the CAP group and 195 ± 5 mm Hg (-20.4% vs. baseline, $P < 0.001$) in the CAP+NIF group. In both groups, the final SBP was significantly lower than that in the untreated CTRL animals ($P < 0.001$, Figure 2).

Echocardiographic data

LV myocardial hypertrophy. Myocardial hypertrophy was determined by the LV_{MA}. The baseline LV_{MA} was in the same range among all of the groups (CTRL, 0.49 ± 0.06 cm²; CAP, 0.55 ± 0.02 cm²; and CAP+NIF, 0.54 ± 0.01 cm²). The CTRL rats showed a mild increase in LV_{MA}, with a peak of 0.60 ± 0.05 cm² at week 16. At that time, the CTRL animals had significantly greater values than the animals receiving antihypertensive therapy; however, over the following weeks, the LV_{MA} in the CTRL group decreased to 0.52 ± 0.02 cm² at week 22. During this time period, two of the CTRL animals died, presenting with final LV_{MA}s of 0.60 and 0.63 cm². CAP therapy reduced the LV_{MA} to 0.46 ± 0.02 cm² (not significant vs. baseline), and

CAP+NIF therapy reduced the LV_MA to $0.47 \pm 0.01 \text{ cm}^2$ ($P=0.005$ vs. baseline; Figure 3a).

LV systolic function. Systolic pump function was evaluated by determining the LV_syst, LV_FAC and CO. In untreated CTRL rats, the LV systolic function decreased, as reflected by a significant increase

in LV_syst over time (baseline: $0.34 \pm 0.03 \text{ cm}^2$, final: $0.58 \pm 0.02 \text{ cm}^2$, $P=0.001$). Antihypertensive treatment attenuated and delayed the deterioration of systolic pump function; LV_syst increased slightly but not significantly from 0.32 ± 0.04 to $0.45 \pm 0.01 \text{ cm}^2$ with CAP therapy and from 0.35 ± 0.03 to $0.43 \pm 0.04 \text{ cm}^2$ with CAP+NIF therapy (Figure 3b).

The LV_FAC decreased over time in all three groups, but the difference was not significant. Among the CTRL animals, it decreased from $46.1 \pm 3.1\%$ at baseline to $36.7 \pm 5.3\%$ at week 22. However, two of these animals had died and presented with clinical signs of LV failure. CAP therapy led to a similar reduction in LV_FAC (from 50.9 ± 5.5 to $40.2 \pm 2.7\%$). The mildest reduction was observed under CAP+NIF therapy (from 48.6 ± 2.9 to $42.6 \pm 2.3\%$; Figure 3c), and no premature deaths were observed in this group.

Similar to LV_FAC, CO decreased slightly but not significantly over time in the untreated CTRLs (baseline, $0.15 \pm 0.011 \text{ min}^{-1}$; final, $0.12 \pm 0.011 \text{ min}^{-1}$; $P=0.59$). A decrease in CO was completely prevented by antihypertensive treatment until week 20 (baseline: CAP, $0.14 \pm 0.011 \text{ min}^{-1}$ and CAP+NIF, $0.15 \pm 0.011 \text{ min}^{-1}$; week 20: $0.16 \pm 0.011 \text{ min}^{-1}$ in both groups; $P=0.004$ vs. CTRL). A slight but not significant decrease was observed at the final measurement ($0.15 \pm 0.011 \text{ min}^{-1}$ in both groups; $P>0.05$ vs. CTRL; Figure 3d).

LV dilatation. LV dilatation was determined by LV_diast. The baseline values of LV_diast were similar in all three groups (CTRL, $0.64 \pm 0.04 \text{ cm}^2$; CAP, $0.66 \pm 0.03 \text{ cm}^2$; and CAP+NIF $0.67 \pm 0.02 \text{ cm}^2$). In CTRL rats, LV_diast continuously increased, and starting at the sixteenth experimental week, it was significantly higher than at baseline. Overall, LV_diast increased by 32.8% (final, $0.85 \pm 0.08 \text{ cm}^2$; $P=0.021$ vs. baseline). Antihypertensive therapy reduced and delayed LV dilatation. A slight increase in the LV_diast of the treatment groups was observed starting at week 16, but it was not significant at any time. The total increase was 13.6% in the CAP group (final, $0.75 \pm 0.03 \text{ cm}^2$) and 10.4% in the CAP+NIF group (final, $0.74 \pm 0.05 \text{ cm}^2$) (Figure 3e).

Hemodynamic data and relative HW

LV catheterization indicated a severe reduction in the LV function of the CTRL animals. While the animals were under anesthesia, we observed a dramatic LV systolic pressure depression to $60 \pm 14 \text{ mm Hg}$. Correspondingly, diastolic aortic pressure decreased to $42 \pm 7 \text{ mm Hg}$. In contrast, in the CAP and CAP+NIF groups, the LV systolic pressure under anesthesia remained at a similar level to that in the awake state (CAP, $172 \pm 11 \text{ mm Hg}$; CAP+NIF, $166 \pm 7 \text{ mm Hg}$), and the diastolic aortic pressure was three times higher than in the CTRL animals ($P<0.001$; Figures 4a and b). The contractility and relaxation parameters (LV dP/dt max and dP/dt min) were two to four times higher in the therapy groups than in the untreated CTRLs ($P<0.001$; Figures 4c and d). Right ventricle function was similar in all three groups (data not shown).

HW was significantly higher in the CTRL animals ($1860 \pm 93 \text{ g}$) than in the treated animals (CAP, $1376 \pm 44 \text{ g}$; CAP+NIF, $1440 \pm 81 \text{ g}$, $P<0.001$). An even greater difference in HW/BW was observed among the groups; while HW/BW reached $4.7 \pm 0.3 \text{ mg/g}$ in the CTRLs, it was only $3.5 \pm 0.2 \text{ mg/g}$ in both of the treatment groups ($P=0.001$ vs. CTRL; data not shown). There were no significant changes in BW over the experimental period. In week 22, the treated animals had a BW of $405 \pm 20 \text{ g}$ (CAP) and $421 \pm 4 \text{ g}$ (CAP+NIF). The BW of the untreated CTRLs, however, tended to decrease ($378 \pm 37 \text{ g}$), particularly among the animals presenting with poor LV function.

Figure 3 Echocardiographic data: (a) left ventricular myocardial area (LV_MA); (b) left ventricular systolic area (LV_syst); (c) left ventricular fractional area change (LV_FAC); (d) cardiac output (CO); (e) left ventricular diastolic area (LV_diast). Data are given as the mean $\pm$ s.e.m. CTRL, untreated SHR (n=4–7); CAP, treatment with captopril (n=6–7); CAP+NIF, treatment with captopril+nifedipine (n=7). Significance marks: □ CAP significant vs. time-matched CTRL; ▲ CAP+NIF significant vs. time-matched CTRL; * CTRL significant vs. baseline (B); ‡ CAP+NIF significant vs. baseline.

Figure 4 Hemodynamic data obtained by heart catheterization at the end of the experimental period (after week 22): (a) left ventricular systolic pressure (LVSP); (b) diastolic aortic pressure (DAP); (c) maximum velocity of left ventricular pressure increase (LV dP/dt max); (d) maximum velocity of left ventricular pressure decrease (LV dP/dt min). The boxes extend from the lower quartile to the upper quartile with the median indicated as a horizontal bar within the box. The whiskers extend from the box to the minimum and maximum values in each sample. The outliers lie more than 1.5 times above or below the interquartile range and are shown as small squares. CTRL, untreated SHR (n=4); CAP, treatment with captopril (n=6); CAP+NIF, treatment with captopril +nifedipine (n=7). Significance marks: * significant vs. CTRL.

DISCUSSION

The results of this echocardiographic study clearly show that untreated long-standing hypertension leads to LV myocardial hypertrophy and LV function deterioration and, consequently, to heart failure and premature death. Antihypertensive treatment, even when started late in life, can delay and attenuate this outcome. Only a few studies have investigated the development of blood pressure in aged SHR on long-term antihypertensive treatment. To the best of our knowledge, the present study is the first to demonstrate the cardiac benefit of a late-onset antihypertensive treatment in SHR using echocardiography.

The SBP of 60-week-old SHR has been found to be significantly higher than that of 7-week-old SHR (170 ± 3 mm Hg) and 7-week-old Wistar-Kyoto rats (WKY; 115 ± 1 mm Hg; $P < 0.001$).⁸ The SBP of WKYs may also increase with age. At 12–17 months of age, the SBP of WKYs has been found to range from 134 to 158 mm Hg.^{17–19} At the age of 20 months, which was the age of the SHR at the end of this experiment, the SBP of WKYs has been found to be 165 mm Hg.²⁰ The results of the present study demonstrate that antihypertensive therapy started at the age of 60 weeks significantly reduced the blood pressure of the SHR. The antihypertensive effects with both therapy regimens were similar; both induced a reduction in SBP by approximately 20% from baseline. However, normotensive values were not achieved under either therapy. The SBP remained approximately 30% above the SBP of the 20-month-old WKYs in the prior study.²⁰ A preliminary study on 7-week-old SHR showed that the same therapy produced a similar relative reduction in SBP but that the absolute SBP values were lower than in the old SHR. At baseline, the

untreated animals in that study had an SBP of 170 ± 3 mm Hg. Over the following 4 weeks, the SBP of the CTRLs significantly increased to 202 ± 6 mm Hg, whereas 4 weeks of antihypertensive treatment with CAP or with CAP+NIF significantly reduced the SBP of the rats to 148 ± 2 mm Hg (–22% compared with the untreated CTRLs) and 152 ± 3 mm Hg (–21% compared with the untreated CTRLs), respectively. However, the SBP values in the CAP and CAP+NIF groups were 22% and 26% higher, respectively, than those of the age-matched WKYs. In contrast, the SBP remained at the baseline level (171 ± 5 mm Hg) with NIF therapy alone; this was 41% higher than the SBP in the age-matched WKYs.⁸ The findings of the present study are in full agreement with those of other studies on adult and senescent SHR. Six weeks of high-dose captopril treatment (100 mg kg^{-1} per day) in 24-week-old SHR reduced their blood pressure by 25% but not to normotensive levels.²¹ Losartan therapy over 8–12 weeks reduced the blood pressure of adult (5–8 months of age) and elderly (17–20 months) SHR by 20–25%.^{18,22} In 65-week-old SHR, 12 weeks of treatment with either enalapril or felodipine reduced blood pressure to a similar extent.²³

However, numerous animal studies using various drugs and doses have demonstrated that an early onset of antihypertensive therapy can be much more effective at reducing SBP and at preventing cardiovascular remodeling. Continuous therapy with either losartan or captopril started at 2–3 months of age resulted in blood pressure normalization after 1 year.^{17,24} Even when it was started at older ages (6–10 months), angiotensin-converting enzyme inhibitor therapy significantly reduced blood pressure.^{5,19} However, withdrawal of therapy led to a partial

reversal of the antihypertensive effects within 4 weeks. Transient captopril treatment (100 mg kg^{-1} per day over 6 weeks) in 4-week-old SHR reduced their blood pressure to normotensive values. This effect was greater than that in rats receiving the same therapy in adulthood (between 24 and 30 weeks of age). Moreover, when captopril was given early in life, significantly lower blood pressure levels persisted even 20 weeks after treatment withdrawal⁵ and were associated with LV hypertrophy prevention and aortic remodeling reduction.⁷ Sustained blood pressure reduction has been assumed to result from decreased sympathetic vasoconstriction and a major therapy-induced reduction of nifedipine-sensitive blood pressure in young SHR. In addition, the withdrawal of captopril therapy induced enhanced vascular remodeling in aged but not in young SHR despite equal doses and treatment duration.⁵

Hypertrophy of the LV is the most important mechanism by which the heart compensates for a chronically elevated blood pressure. It is associated with disproportionate myocyte growth and myocardial remodeling, which results in increased LV wall thickness.²⁵ In the present study, the LV_{MA}, which is a rough measure of mean wall thickness, continuously increased in the untreated SHR starting when they were 60 weeks old until they were 76 weeks old; this indicated the presence of progressive LV hypertrophy. Thereafter, the LV failed to preserve systolic pump function, which was reflected by a significantly elevated LV_{syst}. In experimental week 20, the CO was significantly lower in the untreated rats than in the rats that received antihypertensive treatment, which indicates heart failure in the untreated group. Starting in the sixteenth experimental week, the LV_{diast}, as a measure of LV dilatation, began to significantly increase above the baseline values, which also indicates a transition into LV failure among the untreated rats. Two of the CTRL rats even died during this period and presented with clinical signs of cardiac decompensation. The deterioration of LV function in the CTRL animals became most obvious while they were anesthetized during heart catheterization, and this was reflected by the sharp decreases in LV pressure, contractility and relaxation. Moreover, the *ex vivo* measurement of their HW confirmed the echocardiographic finding of myocardial hypertrophy. These findings are in full accordance with the results of Slama *et al.*²⁶ on long-term LV echocardiographic follow-up in untreated SHR. They also reported myocardial hypertrophy and LV dysfunction in elderly WKYs but to a significantly lower extent than in the SHR in our study.

Antihypertensive treatment continuously reduced the LV myocardial area in the treated rats. This was expected because captopril is known to induce the regression of cardiac hypertrophy.⁹ The decreases in myocardial hypertrophy caused by the two treatments were in the same range; however, a significant effect was only achieved with CAP + NIF treatment. In contrast, the LV diastolic area slightly increased in both of the treatment groups. Although this increase was not significant, it indicates that LV dilatation was not completely prevented, only attenuated and delayed by antihypertensive therapy.

Once structural changes such as LV dilatation have occurred, treatment can delay their progression but not reverse them. This has been confirmed by studies on experimental myocardial infarction in rats and mice. LV dilatation was reduced, and the deterioration of LV function and LV remodeling were attenuated by treatment with either captopril or amlodipine; however, control levels were not achieved.^{27–30} The Systolic Hypertension in Europe (Syst-Eur) study demonstrated that a delay in therapy onset was associated with a significantly higher occurrence of cardiovascular complications.³¹ This finding is in full agreement with our echocardiography and heart catheterization results, which clearly show that antihypertensive

treatment with either a CAP monotherapy or a combination of CAP and NIF delayed cardiac hypertrophy and the deterioration of LV function in SHR but could not completely prevent them.

Limitations of the study

The main limitation of this study is the low number of animals per group. Although the SBP and echocardiographic parameters were highly consistent within the groups, there were large differences in the BW and clinical symptoms of the untreated CTRLs. This indicates high interindividual variation in the tolerance of long-term untreated hypertension, which is also a well-established feature of human pathology.

Another limitation is the lack of a normotensive control group. However, many data exist on the SBP of elderly WKYs (for example, Jülig *et al.*²⁰), which allows for the comparison of our study results with these values. In contrast, the assessment of treatment effects on cardiac remodeling and function is not compromised because our results clearly demonstrate that the late onset of treatment was not able to prevent cardiac hypertrophy and a transition into cardiac failure.

In addition, there may be some methodological limitations concerning the procedure used to measure SBP. The SBP values that were obtained while the animals were awake may have been affected by circadian variation, stress or acute drug effects. To ensure reliable measurements, we used a consistent time regimen for drug application and SBP measurement. Additionally, to minimize stress, the animals were thoroughly familiarized with the experimenters and to the measurement procedure.

Finally, the duration of drug action might have an impact on the efficacy of treatment. Captopril and nifedipine are classical antihypertensive drugs, and their effects on SBP regulation and cardiovascular remodeling in SHR are well-established.^{5,7,9} The antihypertensive effects of these short-acting drugs have been found to be in the same range or even better than those reported from long-acting angiotensin-converting enzyme inhibitors and calcium channel antagonists, such as enalapril, ramipril and felodipine.^{10,23} Therapy with nifedipine alone was left out of our study because a preliminary study on young SHR showed no antihypertensive effects with this treatment.⁸

CONCLUSION

Late-onset antihypertensive therapy in elderly SHR proved to be effective in reducing blood pressure and attenuating cardiac hypertrophy and dysfunction. This finding has particular clinical relevance because hypertension is not diagnosed until advanced age in many patients. Although normotensive values were not achieved in the present study, the SBP of treated SHR was reduced by 20%. Moreover, both treatments preserved LV systolic function over a longer period of time and delayed a transition into heart failure. The efficacy of both treatments was equal with respect to their cardioprotective and antihypertensive effects. These findings underline the importance of antihypertensive treatment in reducing and delaying cardiac failure, even when early therapy onset is not possible and normotensive blood pressure is not achieved.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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