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The Effect of Captopril on the Decrease of Systolic and Diastolic Blood Pressure in Hypertension Rat with Kidney Dysfunction Complications

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Abstract
The most commonly used antihypertensives in Indonesia vary according to the age of the patient. At the age of 40 - 60 years, angiotensin-converting enzyme inhibitor (ACEi) and calcium channel blockers (CCBs) are usually given to older patients. All age groups were treated with a combination of CCB and angiotensin receptor blocker (ARB). Captopril is one of the ACE inhibitor classes, and captopril can lower blood pressure, improve renal impairment, and suppress kidney inflammation through the inactivation of NF-κB in hypertensive mice. Hypertension is closely related to renal dysfunction, requiring blood pressure to be lowered to the normotensive range to prevent progressive kidney damage. In the acute reperfusion stage, captopril prevents excessive angiotensin II synthesis, improves renal dysfunction, inhibited intrarenal inflammation, and better histopathologic findings. Most of the renoprotective effects of captopril occur in the acute reperfusion stage. At the same time, captopril significantly reduces NO availability, exacerbates intrarenal hypoxia, and exacerbates oxidative stress. This study aims to determine the effect of captopril on systolic blood pressure and diastolic blood pressure. In this study, all experimental animals were made hypertensive first by inducing 8% NaCl for 21 days given orally. Then the group with renal complications was induced by administering gentamicin for seven days provided intraperitoneally. Blood creatinine levels were measured using a Photometer5010V5 +. Measurement of systolic blood pressure and diastolic blood pressure using the Non-Invasive Blood Pressure (NIBP) instrument. The data from this study were analyzed using two-way ANOVA. The results showed that complications of renal dysfunction in hypertensive rats had a significant effect on reducing systolic blood pressure and diastolic blood pressure ($p < 0.05$). The administration of captopril at doses of 1.25 mg, 2.5 mg, and 5 mg significantly affected decreased systolic blood pressure and diastolic blood pressure ($p < 0.05$). Captopril 5 mg dose was the most effective in lowering systolic blood pressure and diastolic blood pressure.

Keywords: Captopril, hypertension, systole, diastole, renal dysfunction.

1. Introduction
The most commonly used antihypertensives in Indonesia vary according to the age of the patient. At the age of 40 - 60 years, angiotensin-converting enzyme inhibitor (ACEi) and calcium channel blockers (CCBs) are usually given to older patients. All age groups were treated with a combination of CCB and angiotensin receptor blocker (ARB).[1] ACEi is a blood pressure-lowering that reduces peripheral vascular resistance by inhibiting ACE activity, inhibiting the conversion of angiotensin I to angiotensin II.[2] Captopril is one of the ACE inhibitor classes, and captopril can lower blood pressure, improve renal impairment, and suppress kidney inflammation through the inactivation of NF-κB in hypertensive mice (Spontaneously Hypertensive).[3]

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Hypertension is closely related to renal dysfunction, requiring blood pressure to be lowered to the normotensive range to prevent progressive kidney damage.[4] Hypertension develops in patients with renovascular disease with activation of the renin-angiotensin system (RAS) via oxidative stress and activation of adrenergic sympathies. Although the kidneys maintain function in the autoregulatory range, the continued decrease in renal perfusion results in impaired microvascular function leading to the development of interstitial fibrosis.[5]

It has been shown in several studies that preventing oxidative stress and restoring oxygenation of kidney tissue can inhibit the development of kidney dysfunction. Inhibiting angiotensin II activity, either by inhibiting angiotensin II type 1 receptor or angiotensin-converting enzymes or preventing oxidative stress by administering antioxidants, can control blood pressure. Therefore, tissue hypoxia in the kidneys contributes to the progression of kidney damage and can exacerbate high blood pressure.[6]

In the acute reperfusion stage, captopril prevents excessive angiotensin II synthesis, improves renal dysfunction, inhibited intrarenal inflammation, and better histopathologic findings. Most of the renoprotective effects of captopril occur in the acute reperfusion stage. At the same time, captopril significantly reduces NO availability, exacerbates intrarenal hypoxia, and exacerbates oxidative stress.[7]

Based on the explanation above and the absence of research on the effect of complications of hypertension with renal dysfunction on reducing blood pressure given therapy with captopril, the researchers are interested in researching the impact of captopril on lowering blood pressure in white males rats with hypertensive disease complications of renal dysfunction.

2. Materials and Methods

2.1 Equipment

The equipment used includes the usual stuff in pharmacology laboratories. The instruments used include Triple Beam Balance (OHAUS), Analytical Scale (Precisa), Photometer $5010_{V5+,}$ and CODA® Non-Invasive Blood Pressure (Kent Scientific Corporation).

2.2 Materials

The materials used in this study are Captopril (Kimia Farma), Gentamicin (Kalbe), Propylthiouracil (PTU) (Dexa Medica), Sodium Chloride (Merck), Distilled Water (PT. Brataco), Sodium Carboxymethyl Cellulose (Na CMC) (PT. Brataco), Cholesterol kit reagent (DiaSys®), Creatinine reagent kit (DiaSys®), Hi-Pro-Vite 511 pellet chicken feed (PT. Charoen Indonesia).

2.3 Procedure

2.3.1 Sample preparation

The sample used for this study was captopril with varying doses of 1,25 mg, 2.5 mg, and 5 mg.

2.3.2 Preparation of experimental animals

The experimental animals used were white male rats aged 2-3 months with a 200-250 grams bodyweight, totaling 40 heads. Before being treated, the rats were acclimatized for one week to adapt to their environment. Eating and drinking during maintenance are given sufficiently, and animals are weighed and their behavior observed. The mice used for the experiment were considered healthy; that is, during maintenance, the bodyweight of rats did not decrease more than 10% and visually showed normal behavior.

2.3.3 Preparation of 0.5% Na CMC Suspension

Sprinkle 500 mg of sodium carboxymethyl cellulose in 10 mL of hot water in a hot mortar, leave for 15 minutes, then crush until homogeneous and dilute with distilled water to a volume of 100 mL.

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2.3.4 Preparation of 8% sodium chloride solution
Sodium Chloride (NaCl) is made in concentrations of 8%, whereas much as 8 g NaCl is dissolved in 100 mL of distilled water. NaCl solution is given to mice every day for three weeks orally.[8]

2.3.5 Preparation of gentamicin solution
Preparation of gentamicin solution at a dose of 80 mg/kg BW given intraperitoneally for seven days.

2.3.6 Blood pressure measurement
Blood pressure measurements were carried out using a non-invasive method with the NIBP Tool (CODA). Measurements were made at room temperature. The device used is connected to the CODA application, and the application is activated to start the experiment. Before measuring blood pressure, the Adinstrument Non Invasive Blood Pressure (NIBP) tool that has been connected to a computer is calibrated first. Observation of experimental animals was carried out by measuring blood pressure without anesthesia using the tail-cuff auto-pickup method. The non-invasive way of measuring blood pressure is done with a tail-cuff called a cuff, which contains a Volume Pressure Recorder (VPR) cuff and an occlusion cuff. Rat restraints are performed in a particular place using animal holders. The occlusion cuff uses a disposable rubber attached first to the mouse's tail, followed by the VPR cuff as a pulse detector. The cuff will automatically expand to press the rear of the mice, flowing with blood, and a pulse of blood flow will be detected. The measured pulse was the systolic blood pressure of the mice. Each measurement was carried out ten times for each experimental animal, and then the average was taken. Blood pressure measurement measures systolic blood pressure and diastolic blood pressure. Rats were considered hypertensive when the blood pressure was 140/90 mmHg.[9]

2.3.7 Measurement of creatinine levels
Measurement of creatinine levels was on day eight after induction. Blood was taken from the eyes of mice and collected using a microtube, then left to stand for 15 minutes and centrifuged for 20 minutes at a speed of 3000 rpm. The transparent liquid portion of (serum) is used for the measurement of creatinine levels. The 100 µL serum pipette was added with 1000 µL of mixed creatinine reagent and incubated for 30 seconds. Absorption is measured at a wavelength of 492 nm. For each creatinine determination using a Photometer 5010V5 +, the unit of measurement data in mg/dL. Rats were diagnosed with renal dysfunction when their blood creatinine levels were> 1.1 mg/dL.[10]

3. Results and Discussion
After researching the effect of lowering blood pressure in hypertensive male rats with complications of renal dysfunction, this study included two independent variables. The two independent variables are the dose and time of blood pressure examination. Several dependent variables, namely the percentage reduction in systolic blood pressure and diastolic blood pressure with the drug dose used, were captopril at a dose of 1.25 mg, captopril at a dose of 2.5 mg, and captopril at an amount of 5 mg. While the time of measuring blood pressure at the 1st hour, 2nd hour, and 3rd hour.
From the research done, the results of reducing systolic blood pressure at a dose of 1.25 mg can be seen in Table 1. The impact of decreasing systolic blood pressure at a dose of 2.5 mg can be seen in Table 2. The effect of reducing systolic blood pressure at a quantity of 5 mg can be seen in Table 2. Table 3 and the impact of decreasing diastolic blood pressure at a dose of 1.25 mg can be seen in Table 4. The effect of reducing diastolic blood pressure at a dose of 2.5 mg can be seen in Table 5. The impact of decreasing diastolic blood pressure at a quantity of 5 mg can be seen in Table 6. The average systolic blood pressure of diastolic blood in normal rats and after 8% NaCl induction can be seen in Table 7.
The chart of the decrease in systolic blood pressure at a dose of 1.25 mg can be seen in Figure 1. The graph of the reduction in systolic blood pressure at a dose of 2.5 mg can be seen in Figure 2. The chart of the decrease in systolic blood pressure at a quantity of 5 mg can be seen in Figure 3. The graph of diastolic blood pressure reduction at a dose of 1.25 mg can be seen in Figure 4. The chart of the decrease in diastole blood pressure

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dose of 2.5 mg can be seen in Figure 5. The graph of the reduction in diastolic blood pressure dose of 5 mg can be seen in Figure 6.

Table 1: Effect of reduction in systolic blood pressure at a dose of 1.25 mg based on the treatment group and the length of treatment.

Groups (Dose 1.25 mg)	% Decrease in Systolic Blood Pressure (mmHg)			
	1st hour	2nd hour	3rd hour	Average ± SD
Positive Control	-2,07±0,05	-3,70±0,33	-5,05±0,28	-3,6±1,28[a]
Hypertension	4,73±0,05	7,44±0,082	6,08±0,067	6,08±1,14[b]
Hypertension with Kidney Disfunction	2,27±0,016	3,05±0,021	2,60±0,01	2,64±0,33[c]
Average ± SD	1,88±2,53[p]	2,51±4,09[q]	1,67±4,21[r]	

Note: [a, b, c, p, q, r.] Data with different superscripts in the same column show significant differences (P <0.05).

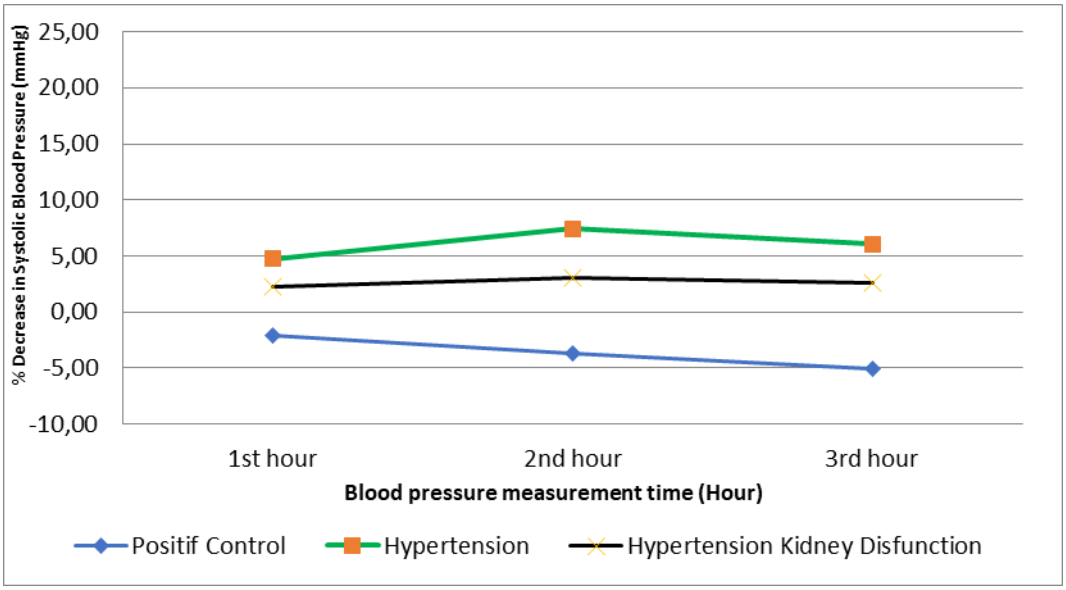

Figure 1: Effect of reducing systolic blood pressure at a dose of 1.25 mg based on the treatment group and treatment duration.

Systolic blood pressure normality test (TDS) dose of 1.25 mg for the control group, hypertension, and hypertension - renal dysfunction with a normality value (P> 0.05) which indicates that the data obtained is usually distributed, then further tests are carried out. In the two-way ANOVA additional test, the treatment group showed a significant value (P <0.05) significantly differently. There was a decrease in TDS based on hypertension and hypertension treatment groups - renal dysfunction, respectively 6.08% and 2.64%, while for the% reduction based on time variations after being induced with captopril 1.25 mg at 1 hour, 2 hours, and 3rd hour respectively 1.88%, 2.51%, and 1.67%.

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Table 2: Effect of reduction in systolic blood pressure at a dose of 2.5 mg based on the treatment group and the length of treatment

Groups (Dose 2.5 mg)	% Decrease in Systolic Blood Pressure (mmHg)			
	1st hour	2nd hour	3rd hour	Average ± SD
Positive Control	-2,07±0,05	-3,70±0,33	-5,05±0,28	-3,60±1,28 [a]
Hypertension	8,73±0,177	10,27±0,30	11,25±0,18	10,08±1,09[b]
Hypertension with Kidney Disfunction	3,64±0,03	4,67±0,04	5,24±0,05	4,52±0,68[c]
Average ± SD	3,84±3,99[p]	4,41±5,24[q]	4,63±6,15[r]	

Note: [a, b, c, p, q, r.] Data with different superscripts in the same column show significant differences (P <0.05).

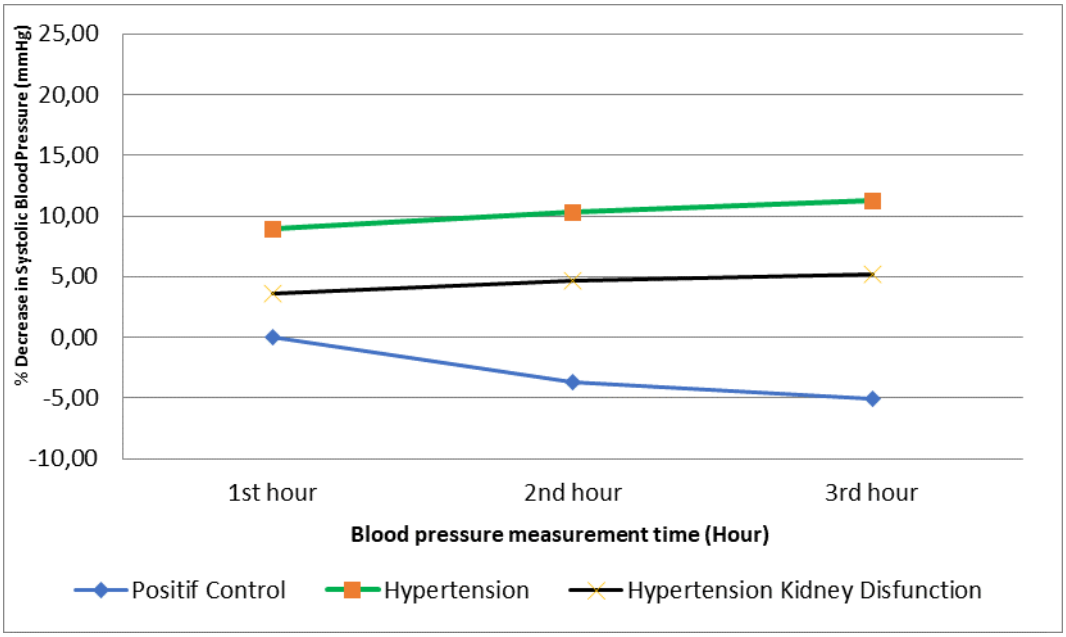

Figure 2: Effect of reducing systolic blood pressure at a dose of 2,5 mg based on the treatment group and treatment duration.

The results of the normality test for systolic blood pressure (TDS) at a dose of 2.5 mg for the control group, hypertension, and hypertension - renal dysfunction with a normality value (P> 0.05) which indicated that the data obtained were normally distributed, then further tests were carried out. In the two-way ANOVA additional test, the treatment group showed a significant value (P <0.05) significantly differently. There was a decrease in TDS based on the hypertension treatment group, and hypertension - renal dysfunction, respectively 10.08% and 4.52%, while for the% reduction based on time variations after being induced with captopril 2.5 mg at 1 hour, 2 hours, and the third hour respectively 3.84%, 4.41%, and 4.63%.

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Table 3{ Effect of reduction in systolic blood pressure at a dose of 5 mg based on the treatment group and the length of treatment

Groups (Dose 5 mg)	% Decrease in Systolic Blood Pressure (mmHg)			
	1st hour	2nd hour	3rd hour	Average ± SD
Positive Control	-2,07±0,05	-3,70±0,33	-5,05±0,28	-3,60±1,28[a]
Hypertension	9,90±0,16	12,13±0,20	12,94±0,22	11,66±1,34[b]
Hypertension with Kidney Disfunction	4,44±0,055	5,71±0,07	7,55±0,094	5,90±1,32[c]
Average ± SD	4,63±4,46[p]	5,63±6[q]	6,20±6,95[r]	

Note: [a, b, c, p, q, r.] Data with different superscripts in the same column show significant differences (P <0.05).

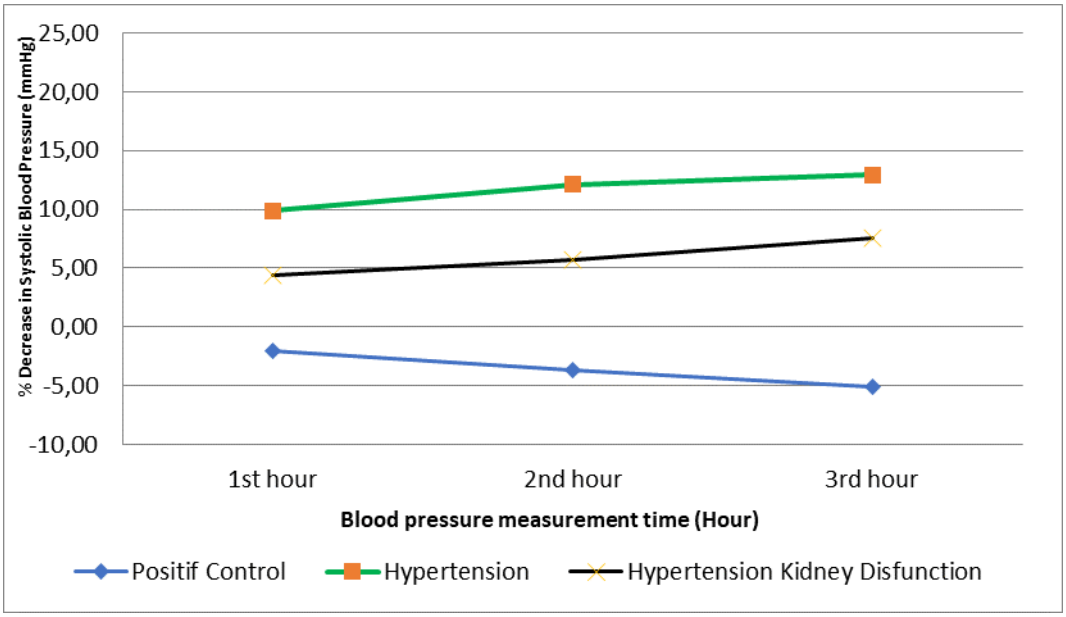

Figure 3: Effect of reduction in systolic blood pressure at a dose of 5 mg based on the treatment group and treatment duration.

The results of the normality test for systolic blood pressure (TDS) at a dose of 5 mg in the control group, hypertension, and hypertension - renal dysfunction with a normality value (P> 0.05) which indicated that the data obtained were normally distributed, then further tests were carried out. In the two-way ANOVA additional test, the treatment group showed a significant value (P <0.05) significantly differently. There was a decrease in TDS based on hypertension and hypertension treatment groups - renal dysfunction, respectively 11.66% and 5.90%, while for the% reduction based on time variations after being induced with 5 mg captopril at hour 1, hour 2, and hour 3, respectively 4.63%, 5.63%, and 6.20%.

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Table 4: Effect of reduction in diastolic blood pressure at a dose of 1,25 mg based on the treatment group and the length of treatment

Groups (Dose 1.25 mg)	% Decrease in Diastolic Blood Pressure (mmHg)			
	1st hour	2nd hour	3rd hour	Average ± SD
Positive Control	-1,76±0,28	-3,45±1,12	-4,72±1,20	-3,31±1,53[a]
Hypertension	6,92±0,31	10,81±0,48	14,38±0,64	10,70±3,18[b]
Hypertension with Kidney Disfunction	3,86±0,06	7,33±0,11	10,04±0,16	7,08±2,61[c]
Average ± SD	3,38±3,27[p]	5,85±5,68[q]	7,94±7,69[r]	

Note: [a, b, c, p, q, r.] Data with different superscripts in the same column show significant differences (P <0.05).

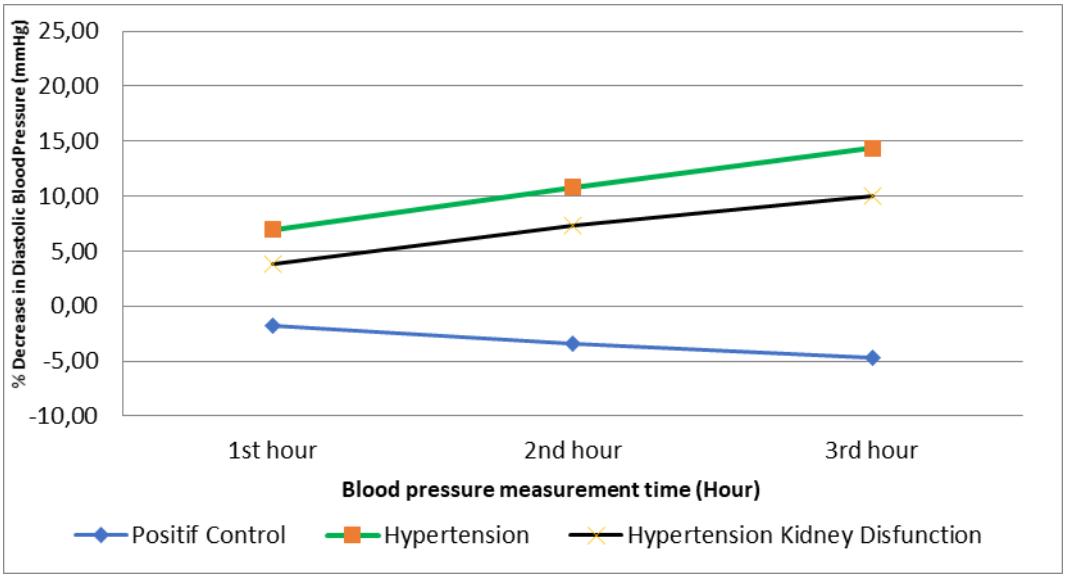

Figure 4: Effect of reduction in diastolic blood pressure at a dose of 1.25 mg based on the treatment group and treatment duration.

The results of the diastolic blood pressure normality test (TDD) at a dose of 1.25 mg for the control group, hypertension, and hypertension - renal dysfunction with a normality value (P> 0.05) which indicated that the data obtained were normally distributed, then further tests were carried out. In the two-way ANOVA additional test, the treatment group showed a significant value (P <0.05) significantly differently. There was a decrease in TDD based on hypertension and hypertension treatment group - renal dysfunction, respectively 10.70% and 7.08%, while for the% reduction based on time variations after being induced with captopril 1.25 mg at hour 1, hour 2, and 3rd hour respectively 3.38%, 5.85%, and 7.94%.

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Table 5: Effect of reduction in diastolic blood pressure at a dose of 2.5 mg based on the treatment group and the length of treatment

Groups (Dose 2.5 mg)	% Decrease in Diastolic Blood Pressure (mmHg)			
	1st hour	2nd hour	3rd hour	Average ± SD
Positive Control	-1,76±0,28	-3,45±1,12	-4,72±1,20	-3,31±1,53[a]
Hypertension	8,20±0,37	12,51±0,57	15,45±0,70	12,05±3,12[b]
Hypertension with Kidney Disfunction	4,21±0,21	8,31±0,41	11,44±0,57	7,98±3,09[c]
Average ± SD	4,12±3,79[p]	6,86±6,33[q]	8,72±8,13[r]	

Note: [a, b, c, p, q, r.] Data with different superscripts in the same column show significant differences (P <0.05).

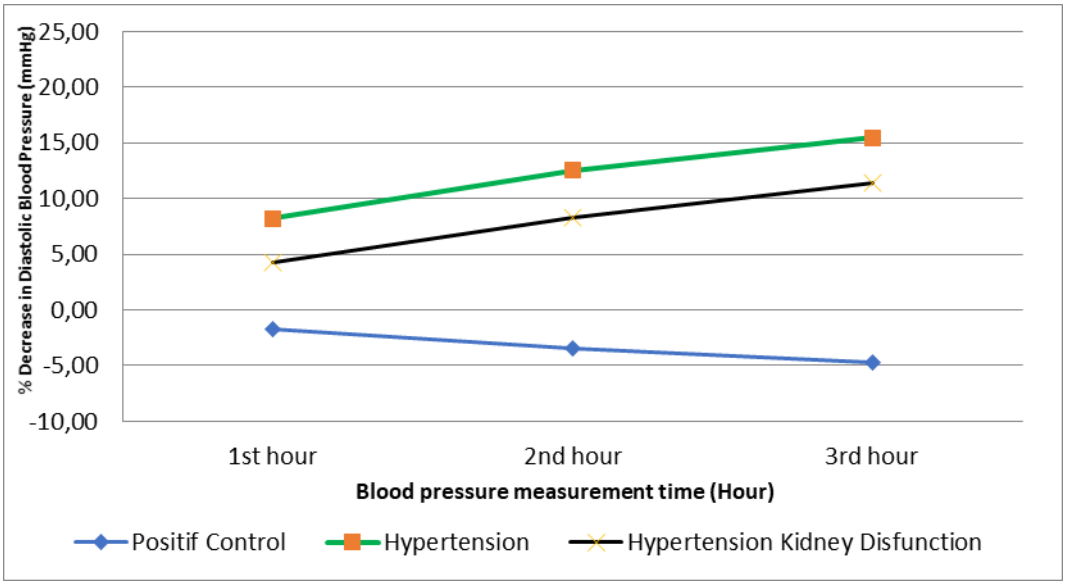

Figure 5: Effect of reduction in diastolic blood pressure at a dose of 2.5 mg based on the treatment group and treatment duration.

The results of the diastolic blood pressure normality test (TDD) at a dose of 2.5 mg for the control group, hypertension, and hypertension - renal dysfunction with a normality value (P> 0.05) which indicated that the data obtained were normally distributed, then further tests were performed. In the two-way ANOVA additional test, the treatment group showed a significant value (P <0.05) significantly differently. There was a decrease in TDD based on hypertension and hypertension treatment groups - renal dysfunction, respectively 12.05% and 7.98%, while for the% reduction based on time variations after being induced with captopril 2.5 mg at 1 hour, 2 hours, and 3rd hour respectively 4.12%, 6.86%, and 8.72%.

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Table 6: Effect of reduction in diastolic blood pressure at a dose of 5 mg based on the treatment group and the length of treatment

Groups (Dose 5 mg)	% Decrease in Diastolic Blood Pressure (mmHg)			
	1st hour	2nd hour	3rd hour	Average ± SD
Positive Control	-1,76±0,28	-3,45±1,12	-4,77±1,20	-3,31±1,35[a]
Hypertension	15,19±0,32	15,59±0,19	16,20±0,34	15,66±0,51[b]
Hypertension with Kidney Disfunction	5,71±0,11	10,82±0,22	14,03±0,29	10,19±3,55[c]
Average ± SD	6,79±6,21[p]	9,00±7,59[q]	10,14±8,85[r]	

Note: [a, b, c, p, q, r.] Data with different superscripts in the same column show significant differences (P <0.05).

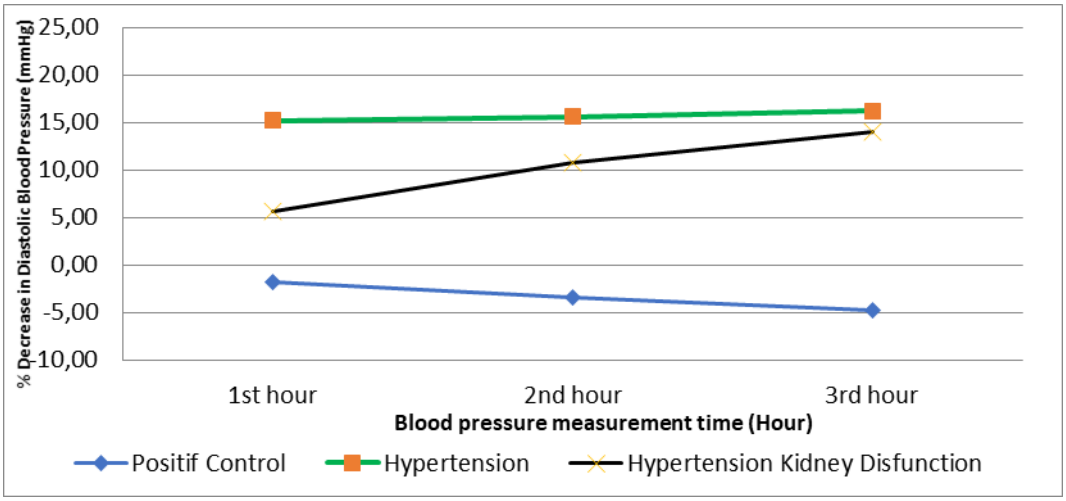

Figure 6. Effect of reduction in diastolic blood pressure at 5 mg based on the treatment group and treatment duration.

The results of the normality test for diastolic blood pressure (TDD) at a dose of 5 mg for the control group, hypertension, and hypertension - renal dysfunction with a normality value (P> 0.05) which indicated that the data obtained were normally distributed, then further tests were carried out. In the two-way ANOVA additional test, the treatment group showed a significant value (P <0.05) significantly differently. There was a decrease in TDD based on hypertension and hypertension treatment groups - renal dysfunction, respectively 15.66% and 10.19%, while for the% reduction based on time variations after being induced with 5 mg captopril at 1 hour, 2 hours, and hour 2 3 respectively 6.79%, 9.00%, and 10.14%.

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Table 7: Average systolic blood pressure and diastolic blood pressure in normal rats and after induction of 8% NaCl.

Groups	Systolic Blood Pressure ± SD (mmHg)	Diastolic Blood Pressure ± SD (mmHg)
Positive Control	117,62 ± 2,13	78,43 ± 3,38
Hypertension	148,38 ± 2,24	95,54 ± 4,17
Hypertension with Kidney Disfunction	155,84 ± 2,14	100,6 ± 3,31

From the research results, systolic blood pressure and diastolic blood pressure in the control group, hypertension, and hypertension - renal dysfunction were significantly different from the normality value (P> 0.05), which indicated that the data obtained were usually distributed. Kidney disease can cause hypertension through the mechanism of increased resistance to blood circulation to the kidneys and decreased glomerular capillary function. This mechanism generates hypoxia in the kidneys and increases renin activity, angiotensinogen, angiotensin I, angiotensin II (ACE), aldosterone, decreased bradykinin, decreased nitric oxide (NO). The increase and decrease in this substance cause vasoconstriction of blood vessels increased peripheral resistance, and increased plasma volume, leading to a rise in blood pressure (hypertension).[11] So that the handling of hypertension in kidney disease must be adequately seen because the two are closely related, where kidney disease can cause hypertension, and persistent hypertension can cause kidney disease to worsen. According to research conducted previously, blood pressure is very influential in decreasing kidney function.[12]

4. Conclusion

From this research, it can be concluded that there is an effect on decreasing blood pressure in rats with various dosages, namely 1.25 mg dose, 2.5 mg dose, and 5 mg dose. The impact of reducing blood pressure in mice was most significant at a dose of 5 mg, and there was also an effect on variations in measurement time. There was a complication effect on reducing blood pressure in rats which was indicated by a minor impact of lowering blood pressure in the hypertensive rats with complications of renal dysfunction compared with the hypertensive rats without complications.

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A Brief Author Biography

Prof. DR. Harrizul Rivai, M.S. was born in Payakumbuh, West Sumatra, on 4 September 1953. His father is Rivai Said, and his mother is Saridahanum Syofyan. The author obtained a Bachelor of Pharmacy from the Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Padjajaran University, Bandung (1976), a Master of Science degree from the Bandung Institute of Technology (1984), and a Doctorate from the Department of Chemistry, Faculty of Mathematics and Natural Sciences, Andalas University, Padang (2011). Now the Author is a Professor and Researcher at the Faculty of Pharmacy, Andalas University, Padang. The author also serves as Deputy Chair of Academic Affairs at the YPTIK Padang College of Pharmacy (STIFARM). The author wrote the book "Principles of Chemical Examination" (Publisher UI-Press, 1995), translated the book "Pharmaceutical Statistics" (EGC Medical Book Publishers, 2010), and wrote "Chapter 4" in the book "Recent Research Advances in Biology Vol. 4" (Book Publisher International, India, and United Kingdom, 2020), and wrote the book "Chinese Petai (*Leucaena leucocephala*): Traditional Uses, Phytochemicals, and Pharmacological Activities" (Deepublish, Yogyakarta, 2021). He wrote “Chapter 9” in the book “Recent Research Advances in Biology Vol. 7" and “Chapters 5, 6, 7, and 8” in the book “Technological Innovation in Pharmaceutical Research Vol. 3 (Book Publisher International, India, and United Kingdom, 2021). The author has also written articles in various international journals in various science fields, such as chemistry, biology, and pharmacy.

