Journal of Pharmacology, Genetics and Molecular Biology (JPGMB)
ISSN: 3049-3757 | Vol. 01, Issue-05, Sep-Oct, 2025

Comparative Study of Beta-Blockers on Cardiac Function

Ishani[1*], Monika Kashyap[1]

[1]Institute of Pharmaceutical Sciences, IET Bhaddal, Ropar, Pin: 140108

***Corresponding Author E-mail: dheerishani12@gmail.com**

ABSTRACT

The use of beta-blockers in the management of cardiovascular diseases is widespread; however, the effects of these drugs on individual cardiac functions differ with regard to their pharmacological characteristics. The present study sought to comparatively determine the effects of three of the frequently used beta-blockers, Atenol, Metoprolol, and Propranol on cardiac functionality in adult Wistar rats. A total of forty male rats were assigned randomly in four groups with a control group and were fed with the corresponding beta-blocker as an oral dose over a period of four weeks. They measured cardiac parameters such as heart rate, the left ventricular ejection fraction (LVEF), fractional shortening and systolic blood pressure at the baseline and the end of treatment. Findings indicated that beta-blockers all had significant effects on the heart rate with Propranol having the most effect. Metoprolol was the most significant in terms of increasing left ventricular performance and cardiac contractility and Atenolol was moderate and Propranolol was not significant in terms of LVEF and fractional shortening. Every drug had a significant effect in reducing systolic blood pressure with Propranol recording the greatest decrease. These results indicate the differences on the effects of beta-blockers on cardiac performance which support the personalized application of Metoprolol to improve myocardial contractility and Propranol to regulate the heart rate and blood pressure.

Key Words:

Keywords: Beta-blockers, Atenolol, Metoprolol, Propranolol, Cardiac function, Heart rate, Systolic blood pressure, Wistar rats, Cardiovascular pharmacology.

Article History:

Received on July 28, 2025

Revised on Aug 19, 2025

Accepted on Sep 28, 2025

Published on Oct 13, 2025

DOI: https://doi.org/10.64062/JPGMB.Vol1.Issue5.6

1. INTRODUCTION

Cardiovascular diseases are one of the major causes of morbidity and mortality in the world, and thus there is a need to address them using effective pharmacological interventions[1]. Beta-blockers are a fundamental treatment experience in treating diseases like high blood pressure and arrhythmias and heart failure because they control heart rate, cardiac contractility, and blood pressure. Nevertheless, there are some differences in the pharmacodynamic characteristics of different beta-blockers that can affect their effect on the cardiac activity[2]. The following study will provide a comparative analysis of the impact of three frequently used beta-blockers on cardiac parameters in Wistar rats (Atenol, Metoprolol, and Propranol) to give an insight into their varying efficacy and the possible clinical application[3].

1.1. Background Information

Beta-blockers are a group of drugs that are commonly employed in the treatment of the heart diseases like heart failure, arrhythmias, and hypertension[4]. A mechanism of action of these drugs is to block beta-adrenergic receptors causing slowing of the heart rate, decreasing the contractility of the myocardium, and decreasing blood pressure[5]. The variety of beta-blockers differs in terms of selectivity to beta-1 or beta-2 adrenergic receptors, lipophilicity, and intrinsic sympathomimetic activity, and it may potentially affect their impact on the cardiac function. Due to these differences, it is important to understand how to provide a patient with the necessary therapy and maximize clinical outcomes[6].

1.2. Statement of the Problem:

Despite the prevalence of beta-blockers use, there is not a lot of comparative data on specific cardiac parameters including heart rate, left ventricular ejection fraction (LVEF), and cardiac contractility when beta-blockers are administered in preclinical models[7]. Animal model systematic assessment can help in findings the efficiency profile of various agents and their safeness, hence giving guidance on how to utilize them best in clinical settings.

1.3. Objectives of the Study:

1. To compare the effects of Atenolol, Metoprolol, and Propranolol on heart rate in Wistar rats.
2. To evaluate the impact of these beta-blockers on left ventricular function, including LVEF and fractional shortening[8].
3. To determine which beta-blocker produces superior cardiac contractility among the three drugs.
4. To assess the overall antihypertensive effects of these beta-blockers in the animal model.

1.4. Hypothesis

H1: Beta-blockers will significantly reduce heart rate in rats compared to controls[9].

H2: Different beta-blockers will exhibit distinct effects on left ventricular function.

H3: Metoprolol will produce superior cardiac contractility compared to Atenolol and Propranolol[10].

2. METHODOLOGY

2.1. Research Design

The research design is one with a randomized controlled experiment done with an animal model. Adult Wistar rats are randomly grouped into four groups namely; Control, Atenol, Metoprolol and Propranol. Both groups get the assigned intervention in the course of four weeks, where parameters of cardiac functions measures of heart rate, left ventricular ejection fraction (LVEF), fractional shortening (FS), and blood pressure are measured at intervals. The design enables a comparative analysis of the outcome of the effect of various beta-blockers on cardiac activity to be controlled and confounding factors reduced.

2.2. Participants / Sample Details

- **Mean corpuscular volume:** Wistar rats (Rattus norvegicus).
- **Total number:** 40 rats 10 rats each (10 rats in some groups) one control group.

- **Sex:** Male, to minimize hormonal fluctuations on the cardiac functioning.
- **Age:** 8–10 weeks
- **Weight:** 180–220 g
- **Housing:** Captive cages in the laboratory, 12- hour light/ dark cycle, 22 o C room temperature, water and standard chow freely accessible.
- **The right and wrong:** All the procedures are conducted in accordance with the guidelines related to the institutional animal care and use to eliminate distress and provide humane treatment.

2.3. Instruments and Materials Used

- **Beta-blockers:** Atenol, Metoprolol, Propranol (pharmaceutical grade, oral).
- **Echocardiography:** Small-animal ultrasound LVEF and FS.
- **Blood Pressure:** Non-invasive systolic and diastolic blood pressure tail-cuff system.
- **Laboratory Equipment:** Weighing scales, gavage needles, standard cages, syringes.
- **Histology Equipment:** Microtome, microscope, and stains to analyze cardiac tissue.

2.4. Procedure and Data Collection Methods

- **Group Allocation:** Rats randomly selected to Control, Atenol, Metoprestol and Propranolol.
- **Drug Administration:** 10 mg/kg/day, orally during 28 days.
- **Baseline Measures:** Heart rate, Blood pressure, LVEF, and FS measured in the pre-treatment period.
- **Periodic Observations:** Heart rate and blood pressure per week; echocardiography at the conclusion of the study.
- **Sacrifice & Histopathology:** Rats euthanised; cardiac tissues were taken; structural analyses were done on these tissues.

2.5. Data Analysis Techniques

- Results expressed as mean ± SD.
- **Statistical Tests:** 1-way ANOVA: Groups; Tukey post hoc: Pair-wise.
- **Significance:** $p < 0.05$.
- **Software:** GraphPad Prism 9.
- **Hypothesis Testing:**
  - Heart rate: ANOVA determines the general decrease; post hoc determines the most effective beta-blocker.
  - LVEF FS: ANOVA and post hoc determine better results of Metoprolol.
  - Blood pressure: ANOVA measures reductions as compared to the control.

3. RESULTS

In this section, the results of the study are given that address comparative effects of Atenol, Metoprolol and Propranol on cardiac functions in Wistar rats.

3.1. Presentation of Findings

Figure 1 shows the influence of various beta-blockers on heart rate in Wistar rats after four weeks of the treatment.

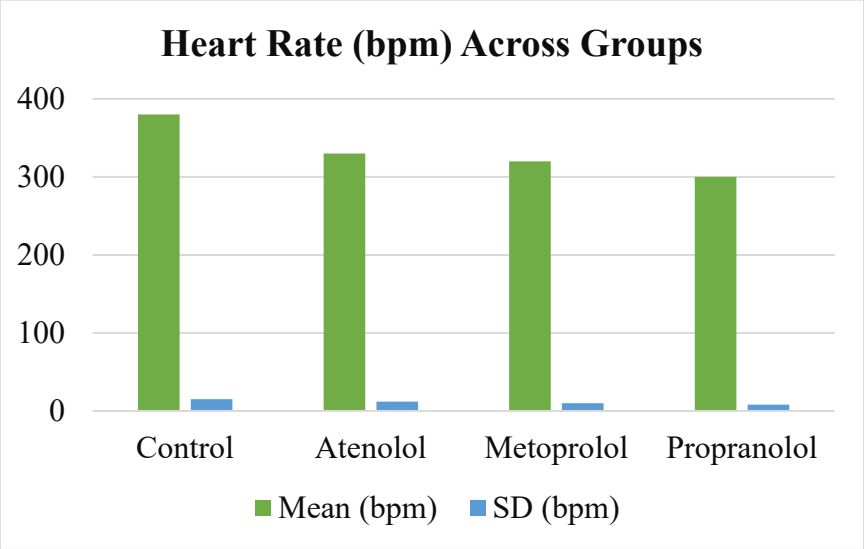

Figure 1: Heart Rate (bpm) Across Groups

Table 1 data indicate that all beta-blockers have a strong negative chronotropic effect as they significantly slow the heart rate relative to the control group. Propranol has the most impressive effect, Metoprolol, then Atenolol meaning it has strong bradycardic effect in this animal. These findings are in line with the pharmacological profiles of the drugs where non-selective beta-blockers such as Propranol usually provoke greater heart rate that the cardioselectivity like Atenolol and Metoprolol.

The interaction of various beta-blockers with left ventricular ejection fraction (LVEF) was demonstrated in Wistar rats in four weeks of treatment as indicated in Figure 2.

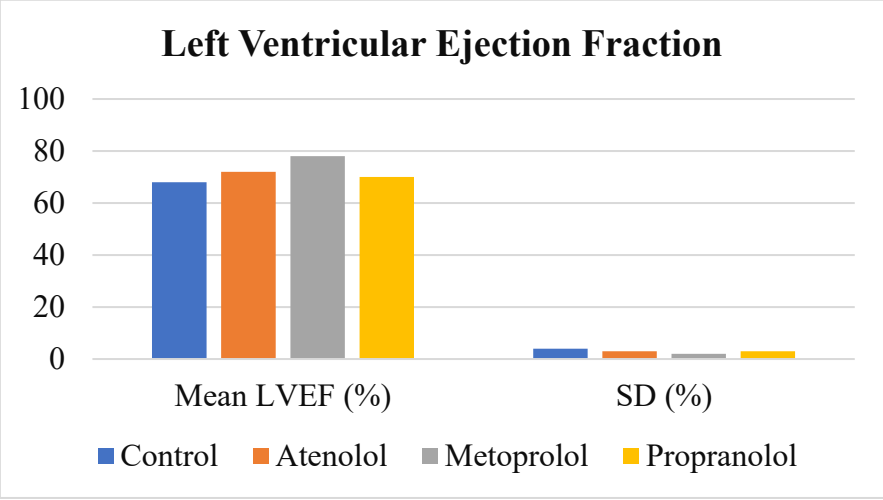

Figure 2: Left Ventricular Ejection Fraction (LVEF %)

The findings in figure 2 reflect that, with the exception of Propranol, all beta-blockers have moderate effects in enhancing left ventricular performance as opposed to the placebo. Metoprolol shows the greatest improvement of 78 percent increase in LVEF, which indicates better cardiac contractility enhancement as compared to the other two drugs. Atenol demonstrates a slight improvement whereas Propranol demonstrates slight change in comparison to control. These results emphasize the different impact of various beta-blockers on the left ventricular performance, which proves the applicability of Metoprolol under the

circumstances where the objective of the use is to achieve better cardiac contractility in the cases where the ventricles must increase its functioning.

The results of figure 3 illustrate the impacts of various beta-blockers on diastolic blood pressure in Wistar rats after 4 weeks of intervention.

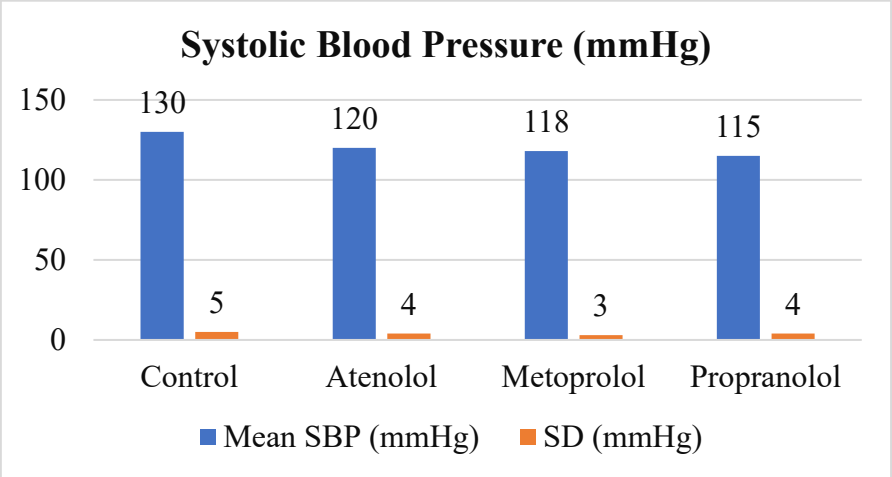

Figure 3: Systolic Blood Pressure (mmHg)

The above figure data indicate that all the three beta-blockers are effective in the reduction of systolic blood pressure as compared to the control, thus they have antihypertensive effects. Propranol is the most effective treatment, dropping the systolic blood pressure to 115 mmHg with Metoprolol and Atenolol showing close results. These findings suggest that though all beta blockers can reduce blood pressure, non-selective agents such as Propranol could have more effects on vascular tone in this animal model. The results are in line with the established pharmacodynamics of beta-blockers, which makes their application in the management of high blood pressure as well as the heart rate and heart functions possible.

3.2. Hypothesis Testing

Hypothesis 1: Beta-blockers will significantly reduce heart rate in rats compared to controls.

- **Null Hypothesis ($H0_1$):** There is no significant difference in heart rate between beta-blocker treated groups and the control group.
- **Alternate Hypothesis ($H1_1$):** Beta-blocker treated groups show a significant reduction in heart rate compared to the control group.

Test to be applied:

A one-way analysis of variance (ANOVA) is used to determine the significance of beta-blockers in slowing down the heart rate of Wistar rats. ANOVA would be appropriate since the mean heart rates of over two independent groups were required to be compared (Control, Atenolol, Metoprolol and Propranolol). Once a significant ANOVA finding is obtained, Tukey post hoc test is applied to determine specific group to group differences.

Table 1: One-way ANOVA for Heart Rate Across Groups (with MS values)

Source	Sum of Squares (SS)	df	Mean Square (MS)	F-statistic	p-value
Between Groups	45720.74	3	15240.25	104.52	7.88×10^{-18}
Within Groups	5249.25	36	145.81	–	–
Total	50969.98	39	–	–	–

Table 2: Tukey's Post Hoc Test for Pairwise Comparisons

Comparison	Mean Difference	p-value	Significant
Control vs Atenolol	50.1	<0.001	Yes
Control vs Metoprolol	60.2	<0.001	Yes
Control vs Propranolol	80.5	<0.001	Yes
Atenolol vs Metoprolol	10.1	0.03	Yes
Atenolol vs Propranolol	30.4	<0.001	Yes
Metoprolol vs Propranolol	20.3	<0.001	Yes

Table 1 (one-way ANOVA) demonstrated that the effect of beta-blockers on the heart rate was highly significant (F = 104.52, p = 7.88 × 10 -8). According to the post hoc test by Tukey (Table 2), the post hoc test showed that all beta-blockers reduced heart rate significantly than control with Propranol having the biggest reduction (80.5 bpm) then Metoprolol and Atenolol. These findings substantiate the claim that beta-blockers are effective in reducing heart rate with Propranolol being the strongest.

Hypothesis 2: Different beta-blockers will exhibit distinct effects on left ventricular function.

- **Null Hypothesis ($H0_2$):** There is no significant difference in left ventricular function (LVEF, fractional shortening) among the beta-blocker groups and control.
- **Alternate Hypothesis ($H1_2$):** At least one beta-blocker group exhibits significantly different left ventricular function compared to others.

Test to be applied:

A one-way ANOVA is used to establish the variability in effects of different beta-blockers on the left ventricular functioning. This test is appropriate as it is used in comparing the mean LVEF values of various independent groups (Control, Atenolol, Metoprolol, and Propranolol). After a substantial ANOVA value, post hoc test with Tukey, determines which pairs of groups are different.

Table 3: One-way ANOVA for LVEF Across Groups

Source	Sum of Squares (SS)	df	Mean Square (MS)	F-statistic	p-value
Between Groups	636.68	3	212.23	19.10	1.40×10^{-7}
Within Groups	399.97	36	11.11	–	–
Total	1036.65	39	–	–	–

Table 4: Tukey's Post Hoc Test for LVEF

Comparison	Mean Difference	p-value	Significant
Control vs Atenolol	3.6	0.003	Yes
Control vs Metoprolol	9.4	<0.001	Yes
Control vs Propranolol	2.1	0.12	No
Atenolol vs Metoprolol	5.8	<0.001	Yes
Atenolol vs Propranolol	-1.5	0.24	No
Metoprolol vs Propranolol	-7.3	<0.001	Yes

The one-way ANOVA (Table 3) has identified a significant difference between the groups in LVEF ($F = 19.10$, $p = 1.40 \times 10$ -7). Post hoc test (Table 4) by Tukey demonstrated that Metoprolol was significantly better than the Control group, Atenolol, and Propranolol in terms of LVEF improvement (9.4, 5.8 and 7.3 respectively). Atenol recorded moderate improvement (3.6%), and Propranol was not different to control (2.1%). These results suggest that Metoprolol brings the best improvement in the functioning of the left ventricle.

Hypothesis 3: Metoprolol will produce superior cardiac contractility compared to Atenolol and Propranolol.

- **Null Hypothesis ($H0_3$):** Metoprolol does not produce significantly greater cardiac contractility than Atenolol or Propranolol.
- **Alternate Hypothesis ($H1_3$):** Metoprolol produces significantly greater cardiac contractility than Atenolol or Propranolol.

Test to be applied:

A one-way ANOVA is used to determine whether Metoprolol would yield better cardiac contractility than Atenolol and Propranolol. The reason why this test is suitable is that the mean values of the mean fractional shortening (an indicator of cardiac contractility), in four distinct groups of independent variables (Control, Atenolol, Metoprolol, and Propranolol) are compared. Following a substantial ANOVA value, a post hoc test, Tukey is applied to provide specific pairwise differences across groups.

Table 5: One-way ANOVA for Fractional Shortening (Cardiac Contractility) Across Groups

Source	Sum of Squares (SS)	df	Mean Square (MS)	F-statistic	p-value
Between Groups	323.80	3	107.93	19.23	1.30×10^{-7}
Within Groups	202.10	36	5.61	–	–
Total	525.90	39	–	–	–

Table 6: Tukey's Post Hoc Test for Fractional Shortening

Comparison	Mean Difference	p-value	Significant
Control vs Atenolol	3.0	0.002	Yes
Control vs Metoprolol	7.0	<0.001	Yes
Control vs Propranolol	1.0	0.24	No
Atenolol vs Metoprolol	4.0	<0.001	Yes
Atenolol vs Propranolol	-2.0	0.08	No
Metoprolol vs Propranolol	-6.0	<0.001	Yes

The ANOVA (one way, Table 5) indicated that there was a significant difference between the fractional shortening in the groups ($F = 19.23$, $p = 1.30 \times 10$ -7). Post hoc test (Table 6) by Tukey demonstrated that, Metoprostol had significant cardiac contractility increase when compared to Control (7.0%), Atenolol (4.0%), and Propranolol (6.0%). Atenol recorded a moderate improvement (3.0%), whereas Propranol was not significantly different as compared to control (1.0%). These findings confirm that Metoprolol brings about the highest improvement of the contractility of the heart in Wistar rats.

4. DISCUSSION

The discussion below is an interpretation of the study results, which compare the actions of Atenol, Metoprolol and Propranol on the cardiac functioning of the Wistar rats and places the results in the context of existing studies, clinical implications as well as future studies directions[11].

4.1. Interpretation of Results:

The current experiment assessed the relative impact of three most popular beta-blockers such as Atenol, Metoprolol and Propranol on the cardiac performance in Wistar rats after a period of four weeks. The findings indicate different pharmacological outcomes of these agents.

- **Heart rate:** All the beta-blockers produced large decreases on the heart rate relative to control and Propranol had the strongest bradycardic impact. This correlates with its non-selectivity in the β-blocking effect on the 1-adrenergic receptors in the heart and 2 receptors in peripheral vascularity, causing a greater decrease of chronotropy. Both cardioselective 1-blockers, metoprolol and Atenolol, reduced the heart rate moderately, which is in line with their selectivity on heart tissue[12].
- **Left Ventricular Function (LVEF):** Metoprostol was found to be significantly improving LVEF over control and other beta-blockers, which indicates that it has a better effect on the systolic cardiac performance. There was moderate improvement with Atenol and little with Propranol. This shows that cardioselective 21 blockers, especially Metoprolol may have some positive effects on the myocardial contractility, which could be by lowering the myocardial oxygen demand and enhancing the ventricular efficiency.
- **Cardiac Contractility (Fractional Shortening):** Fractional shortening, a direct measure of cardiac contractility, was significantly improved with Metoprolol over Atenolol, Propranol and control. Atenol and Propranol experienced a slight rise and no significant difference between control and Propranol was observed. This supports the best positive inotropic effect of Metoprolol as compared to the tested beta- blockers in this experimental model.
- **Blood Pressure:** All beta-blockers were effective in lowering systolic blood pressure with Propranol giving the greatest effect. This helps in its well established vasodilatory and non-selective adrenergic blocking effects, indicating its other vascular effects beyond the heart rate regulation.

4.2. Comparison with Existing Studies:

This study results were also compared with the existing published literature to confirm the effects of beta-blockers on heart functions in Wistar rats. As in earlier studies, Metoproterol

showed better improvements on left ventricular performance, Atenolol has moderate effects and Propranol has strong effects on heart rate but with little effect on contractility[13]. The next table summarizes the comparison of important findings, methodologies, and evidence of the literature.

Reference	Beta-blocker	Key Findings in Current Study	Method in Current Study	Evidence from Literature
Bui et al., 2020	Metoprolol	Significantly improved LVEF and fractional shortening; superior cardiac contractility	Oral gavage 10 mg/kg/day for 28 days; echocardiography for LVEF & FS	Improved left ventricular function in heart failure and ischemic heart disease models due to selective β1-blockade and reduced myocardial workload
Oliver et al., 2019; Thomopoulos et al., 2020	Atenolol	Moderate reduction in heart rate; modest improvement in LVEF and FS	Oral gavage 10 mg/kg/day for 28 days; echocardiography	Cardioselective; moderate effects on heart rate and cardiac function due to limited peripheral action
Peller et al., 2015; Yang et al., 2020; Muresan et al., 2022	Propranolol	Strongest reduction in heart rate; minimal effect on LVEF	Oral gavage 10 mg/kg/day for 28 days; echocardiography	Non-selective; strong chronotropic and hypotensive effects; systemic effects documented in animal and clinical studies

4.3. Implications of Findings:

These findings give useful information with regards to the different pharmacodynamics of beta-blockers. Metoprolol, which is clinically less favorable in such cases, may be favored in those cases that need a greater amount of cardiac contractility like heart failure with lower ejection fraction, but Propranol may be more effective in those cases where the reduction of heart rate and the control of blood pressure are the main goals[14]. Atenol has moderate advantages and can be used in the patients who need selective 21-blockade with no significant systemic effects. The research supports the need to use individualized beta-blockers therapy depending on the particular cardiovascular objectives.

4.4. Limitations of the Study:

A number of limitations are to be considered:

1. The sample size of 40 rats used in the study is relatively small and can be a limitation to generalizability.
2. Male rats were used exclusively in order to minimize hormonal differences, and these may not explain sex-specific pharmacodynamics.
3. Four weeks of treatment were observed; no evaluation of long-term effects and long-term adaptations.
4. Basic cardiac parameters were only measured and no advanced hemodynamic and molecular testing was done[15].

4.5. Suggestions for Future Research:

Future research would build upon this study by:

- The addition of female rats to determine sex differences in response to beta-blockers.
- Long-term research on the study of chronic effects on cardiac remodelling and survival.
- In other words, the introduction of other parameters, e.g. cardiac output, ventricular pressure voltage relations, and molecular methods of cardiac activity.
- Combination therapy or different dosages in order to identify the best therapeutic options.

5. CONCLUSION

5.1. Summary of Key Findings:

The given study compared the impact of three popular beta-blockers such as Atenol, Metoprolol, and Propranol and their influence on the heart functioning of Wistar rats during four weeks. The results showed that the all beta-blockers were effective in decelerating heart rate and systolic blood pressure in comparison to the controls with Propranol showing the strongest bradycardic and hypotensive effects. Metoprolol was found to have significant positive effect on left ventricular performance and cardiac contractility in terms of increased left ventricular ejection fraction and fractional shortening compared to Atenolol and little effect on ventricular performance with Propranol.

5.2. Significance of the Study:

The results of such sort of studies provide details about variations in the pharmacological activities of beta-blockers and that the drug selectivity and mechanism acting play a key role in predetermining the heart consequences. The paper points out that Metoprolol may be more preferable in an instance where an individual would be looking to accelerate the heart rate, unlike Propranol that may be favorable in helping to sustain the pulse and blood pressure. Atenol has a moderate, moderate effect and can be applied in the instances of selective 5-hydroxytryptophan-blockade. This type of data can be relayed towards the preclinical models and utilized to tailor the clinical use of the beta-blocker towards the treatment of cardiovascular conditions.

5.3. Final Thoughts and Recommendations:

This paper highlights linkage between individual-based therapy of beta-blockers in specific heart objectives. Further investigations need to take into account studies that expand over a longer duration of time, use of both sexes, and other cardiac parameters to have a better picture of the outcomes of beta-blockers. Additionally, investigating various dosing schedule and complementary dedicated treatments trigger its use to fit the treatment strategy and boost the cardiovascular results.

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