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Effects of cardiovascular drugs on cardiac physiology in rabbits: A comprehensive review of experimental studies

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Abstract
Cardiovascular diseases (CVDs) remain the leading cause of mortality worldwide, driving the continuous search for effective pharmacological strategies. Experimental animal models are essential for elucidating drug actions on cardiac physiology, bridging preclinical research and human application. Among these, the rabbit (*Oryctolagus cuniculus*) has become a translationally relevant species due to its electrophysiological and metabolic similarities to humans. This comprehensive review synthesizes experimental findings on how major cardiovascular drug classes β-adrenergic blockers, calcium-channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), nitrates, statins, and diuretics affect cardiac physiology in rabbits. Evidence from *in vivo* and *ex vivo* models demonstrates consistent modulation of heart rate, contractility, oxidative stress, and myocardial remodeling. Molecular and histological studies reveal that these agents influence apoptosis, fibrosis, and mitochondrial integrity, highlighting complex cardioprotective mechanisms beyond their primary hemodynamic actions. Despite interspecies differences in pharmacokinetics and enzyme profiles, the rabbit model remains indispensable for preclinical cardiovascular pharmacology. Future studies integrating molecular imaging, omics platforms, and chronic exposure protocols will further enhance translational predictability and therapeutic relevance.

Keywords: β-blockers, ACE inhibitors, cardiac physiology, rabbit model, cardiovascular drugs, calcium-channel blockers, statins, myocardial remodeling, oxidative stress

Introduction
The burden of CVDs in terms of incidence and prevalence is about one-third of all deaths all over the world and the economic and public-health costs are staggering (Kabakov *et al*., 2021; Pogwizd and Bers, 2008) [12, 22]. To understand the mechanisms of action of drugs on the heart, we have to know physiology, in order to develop new therapeutic agents and to improve the extinguish the existing ones. Preclinical animal models provide a very important interface between molecular pharmacology and clinical practice. The most useful of them is the rabbit (*Oryctolagus cuniculus*), which, due to its myocardial structure, heart rate, and electrophysiological characteristics, is more reminiscent of human ones than small rodents (Ellermann *et al*., 2021; Joukar *et al*., 2021) [4, 11]. Action potentials of rabbits have a plateau-repolarization profile and corresponding human ventricular cells (Kabakov *et al*., 2021) [12]. Their intermediate heart rate (180 to 300 bpm) can be reliably used to determine contractility and arrhythmogenic potential. The rabbit ventricular myocyte and the Langendorff-perfused heart have been proven to be predictable preparations of the excitation contract coupling, calcium regulation, and proarrhythmia due to drugs (Rozanski *et al*., 1997) [25].
A number of studies has proved versatility of the model. Indicatively, Mahaffey *et al*. (1995) [16] recreated post-infarction remodeling using coronary ligation whereas Gonzalez *et al*. (2016) demonstrated that the prevention of diastolic dysfunction was achieved using early ACE-inhibitor therapy. Raine *et al*. (1981) [24] defined 8 3-receptor adaptation following a long-term 8 3-blockade, and Hill *et al*. (2001) [9] revealed late ischemic preconditioning through nitroglycerin.

Altogether these studies bring out the translationality of the rabbit in both mechanistic and therapeutical cardiology. This is a review of more than forty years of experimental literature that gives a compilation of evidence regarding the effects of cardiovascular drugs on cardiac physiology in rabbits. They are hemodynamic, electrophysiological, molecular, and histological responses to major classes of drugs, and translational and methodological considerations on future research (Baron *et al*., 2024; Frommeyer *et al*., 2019; Niimi *et al*., 2020) [1, 5, 19].

2. The Rabbit as an Experimental Model

2.1 Physiological and Experimental Features

The rabbit heart exhibits aspects of electrophysiological performance, which closely resembles the human heart. The L-type calcium and delayed-rectifier potassium currents have a similar relative contribution to each other as in human myocardium, which supports the translation of the repolarization and arrhythmogenesis models (Kabakov *et al*., 2021; Pogwizd & Bers, 2008) [12, 22]. The Langendorff-perfused rabbit heart provides the possibility of direct measuring of the left-ventricular pressure, the coronary flow, and arrhythmic events (Baron *et al*., 2024; Lawrence *et al*., 2006) [1, 15]. The moderate size of rabbits supports them to be chronically instrumented, injected intravenously, and serially echocardiographed. Moreover, the lipid and glucose metabolism of rabbits is similar to those of humans, and thus they can be used to study atherosclerosis and metabolic cardiomyopathies (Niimi *et al*., 2020; Shiomi *et al*., 2013) [19, 28]. Human cardiac protein transgenic rab bit lines, have been used to expand mechanistic studies on arrhythmias and remodelling (Hornyik *et al*., 2022).

2.2 Advantages and Applications

Rabbit models are used to fill the gap of rodent to large animal species. They are especially appropriate to test QT prolongation and torsade de pointes risk caused by drugs (Carlsson, 2008; Vincze *et al*., 2007). They can reproduce myocardial infarction exactly because of their coronary anatomy through coronary ligation, or microsphere embolization (Mahaffey *et al*., 1995; Morrissey *et al*., 2017). Also, the Watanabe heritable hyperlipidemic (WHHL) rabbit is also used as classical model of statin and anti-atherosclerotic drugs (Shiomi, 2009; Takagi *et al*., 1997) [27, 28, 30].

2.3 Limitations

Although they have many benefits, rabbits have elevated basal heart rates and unique cytochrome P450 isoenzyme, which has an influence on pharmacokinetic predictability (Pogwizd & Bers, 2009) [22]. Variations can be brought about by anesthetic procedures and differences in strains (Yang *et al*., 2025) [34]. However, experimental design optimization and high-quality imaging, including cardiac MRI, proteomics, etc., are improving the reproducibility and translational accuracy (Wu *et al*., 2022) [33].

3. Classes of Cardiovascular Drugs and Their Effects

3.1 β-Adrenergic Blockers

β-blockers are the cornerstones in cardiovascular treatment, whose effects work mostly by β1-receptor blocking and lowering myocardial oxygen requirement. Chronic propranol use in rabbits reduces left-ventricular developed pressure and heart rate and augments the relaxation time of the diastole (Raine *et al*., 1981; Wiktorowska-Owczarek *et al*., 2000) [24, 32]. 0-Blockade also normalizes the calcium cycling by regulating the expression of SERCA2a and phospholamban (Pogwizd & Bers, 2008) [22]. The experimental evidence suggests that 2-blockers prevent post-infarction arrhythmias by stabilizing repolarization and inhibiting cellular 2-catecholamine induced early after-depolarizations (Rozanski *et al*., 1997) [25]. These results are in agreement with clinical anti-arrhythmic effects in human beings (Frommeyer *et al*., 2019) [5].

3.2 Calcium-Channel Blockers

L-type Ca 2 + currents are blocked by calcium-channel blockers (CCBs), including verapamil and diltiazem, which cause negative inotropy and bradycardia. In Langendorff-perfused rabbit hearts experiments, there is dose-dependent contraction and conduction expansion of atrioventricular conduction (Seguchi *et al*., 1986; Stams *et al*., 2012) [26, 29]. CBBs decrease the size of infarctions and maintain the mitochondrial architecture in models of ischemia-reperfusion (Kim *et al*., 1988) [13]. Withdrawal of CCB in rabbits over a long period prevents cytoplasmic vacuolization as well as nuclear pyknosis and is possibly cytoprotective (Pinelli *et al*., 2010) [21]. These effects are similar to the improvement in diastolic filling and decreased oxidative stress that have been recorded in clinical situations.

3.3 ACE Inhibitors and ARBs

The prevention of post-infarction remodeling is based on the use of ACE inhibitors (e.g., captopril, enalapril) and ARBs (e.g., losartan). Early administration of enalapril prevents the deposition of collagen, up-regulates eNOS, and oxidative damage in rabbits (González *et al*., 2016) [8]. The same effect is applied by Losartan, which enhances the compliance in the diastole and restricts fibrosis. In a study by Yoshiyama *et al*. (2005) [35], the normal geometry and contractility of the ventricles were recovered through ACE inhibition following myocardial infarction. Apoptosis and angiogenesis are other effects of these agents by down-regulating Bax and caspase-3 and up-regulating Bcl-2 and VEGF. Their effects of pleiotropic antioxidants are seen through reduction in malondialdehyde, and increase in superoxide-dismutase.

3.4 Nitrates and Vasodilators

Organic nitrates stimulate the nitric-oxide release and activates the action of soluble guanylate cyclase and cGMP-dependent signaling. Nitroglycerin reduces the left-ventricular wall stress in rabbits without impairing the coronary perfusion (Fukuyama *et al*., 1980; Hill *et al*., 2001) [6, 9]. NO exogenous donors reduce the duration of action-potential and inhibit arrhythmia caused by ischemia (Baron *et al*., 2024) [1]. Prolonged administration of nitrates produces late preconditioning with a decreased infarct size through phosphorylation of troponin I by PKG (Hill *et al*., 2001) [9].

3.5 Statins and Antioxidant Agents

Statins have strong cardioprotective properties other than lowering lipid. Atorvastatin and simvastatin lower vascular inflammation, improve endothelial relaxation and myocardial perfusion in WHHL rabbits (Bustos *et al*., 1998; Shiomi *et al*., 2013) [2, 28]. Other beneficial effects on human clinical outcomes are that statin therapy reduces oxidative stress and up-regulates eNOS (Niimi *et al*., 2020) [19].

Antioxidants such as coenzyme Q10 and N-acetylcysteine, tested in rabbits, reduce lipid peroxidation and preserve mitochondrial ultrastructure during ischemia (Lai *et al*., 2011)

[14]. These findings suggest synergistic protection when antioxidants complement conventional drugs.

3.6 Diuretics and Other Agents

Diuretics have an indirect effect on cardiac workload through alterations in preload and electrolyte balance. In rabbits, furosemide and hydrochlorothiazide research indicates moderate hypotension and myocardial excitability change (Pogwizd & Bers, 2008) [22]. They improve hemodynamic stability and decrease the pulmonary congestion, which is in line with the human clinical practice when used together with 8-blockers or ACE inhibitors.

4. Molecular and Histological Changes

4.1 Biochemical Responses

Biochemical modulation by cardiovascular drugs is always demonstrated in experimental rabbit models. ACE inhibitors reduce serum CK-MB and LDH release after infarction, whereas 2-blockers reduce the release of troponins and oxidative biomarkers (Raine *et al*., 1981) [24]. The calcium-channel blockers and nitrates elevate the activities of antioxidant enzymes (Hill *et al*., 2001) [9]. Statins increase eNOS and inhibit NF-kB activation and associate metabolic maintenance with endothelial defense (Bustos *et al*., 1998; Ellermann *et al*., 2021) [2, 4].

4.2 Molecular Pathways

ACE inhibitors or ARBs mitigate apoptosis in rabbits via the attenuation of the Bcl-2/Bax ratios and caspase cascade. Blociston of calcium-cycling proteins (SERCA2a, phospholamban) is observed with β-blockers, whereas transcription of inflammatory cytokines is prevented with statins (Shiomi, 2009) [27]. NO donors stimulate the cGMP-PKG, phosphorylate contractile proteins, and decrease calcium sensitivity (Baron *et al*., 2024) [1]. The up-regulation of VEGF and eNOS is verified by gene-expression profiling, which is expected with the angiogenic and vasoprotective remodelling (Wu *et al*., 2022) [33]. These convergent processes are the reasons as to why there are integrated biochemical and morphological advantage seen in animals treated to drugs.

4.3 Histopathological Findings

The untreated infarcted rabbits show signs of necrosis, infiltration, and fibrosis (Mahaffey *et al*., 1995; Pinelli *et al*., 2004) [16, 20]. These changes are significantly reduced by drug therapy. ACE-inhibitors and 2-blockers decrease fibrotic space and rebuild myocardial structure (Yoshiyama *et al*., 2005) [35]. CCBs inhibit the swelling and the disorganization of the sarcomeres located in the mitochondrion (Kim *et al*., 1988) [13]. Statins and antioxidants maintain the integrity of endothelium and inhibit lipid deposition in the coronary vessel (Shiomi *et al*., 2013; Niimi *et al*., 2020) [28, 19]. Nifedipine therapy results in better mitochondrial cristae and intercalated-disc continuity by electron microscopy, which confirms the structural preservation in line with biochemical results (Baron *et al*., 2024) [1].

5. Translational Significance

Rabbit models predict so well because they have close similar physiological features with the human heart. The proarrhythmic or protective results can be correctly predicted based on similar action-potential patterns and ion-channel distributions (Rozanski *et al*., 1997; Carlsson, 2008) [25, 3]. The rabbit is therefore a control measure of preclinical QT-prolongation testing (Lawrence *et al*., 2006) [15]. The research on rabbits has had a direct impact on human therapeutics: anti-fibrotic effects of enalapril and preconditioning effects of nitroglycerin (Hill *et al*., 2001) [9] are similar to the clinical outcomes. In the same way, endothelial recovery of WHHL rabbits with statins predicted similar vascular benefits in patients (Shiomi *et al*., 2013) [33]. However, the variation in the drug metabolism in species makes extrapolation risky. Pharmacodynamics may change in response to different P450 isoforms and heart rate differences (Pogwizd & Bers, 2009) [23]. Anesthesia, strain, and sex also vary, which also affects reproducibility (Yang *et al*., 2025) [34]. The use of the newest imaging, multi-omics, and computational modeling will improve the level of translational accuracy (Mačianskienė *et al*., 2018; Hornyik *et al*., 2022) [17, 10]. This model has demonstrated its timeless applicability in cardiovascular pharmacology primarily because the rabbit data is integrated with human clinical findings in a continuum, which has consequently become known as the mechanistic discovery and therapeutic validation.

6. Conclusion and Future Directions

Studies in the last 50 years have solidly entrenched the use of the rabbit as a model species to develop the impact of cardiovascular drugs. Rabbits have led to the understanding of the mechanisms through which pharmacologic agents may affect myocardial contractility, conduction, and remodelling by complementary *in vivo* and *ex vivo* studies (Pogwizd & Bers, 2008; Ellermann *et al*., 2021) [22, 4]. The reliability of the model is testified by the consistent reduction of oxidative stress, apoptosis, and fibrosis in a variety of drug classes (González *et al*., 2016; Baron *et al*., 2024) [8, 1]. Future studies should focus on chronic exposure and combination-therapy regimens, as they are a representation of real clinical regimens. The implementation of molecular imaging, genomics, and proteomics will disclose the new biomarkers of drug action to long-term structural adaptation. Reproducibility will be further enhanced by standardization of experimental design and transparent reporting as well as inter-study comparison. To conclude, the rabbit model has been a mainstay in experimental cardiology, providing a physiological model of humans with a unique combination of experimental accessibility. Its further application is bound to enhance the knowledge about cardiovascular pharmacodynamics and enable the production of safer and more efficient treatment.

Conflict of Interest

Not available

Financial Support

Not available

Reference

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