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Review Article

New Drug Discovery of Anti-Congestive Heart Failure agents: Insights in Animal Models

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Abstract

Congestive heart failure (CHF) is a long-term medical illness in which the heart cannot pump enough blood to meet the body's metabolic needs. Symptoms like exhaustion, shortness of breath and fluid build-up in the lungs and other organs. Numerous conditions, such as coronary artery disease, hypertension, valvular heart disease and cardiomyopathy are the main causes. Several models are developed to address cardiovascular complications, including coronary artery ligation, cardiac hypertrophy and cardiac diseases, and the same pathology is successfully recreated in different species. The animal models of CHF, their characteristics and their significance summarized as: In-vitro methods: Isolated Hamster Cardiomyopathic heart, Isolated Rat Papillary Muscle and Ouabain binding. In-vivo methods: Rat Models of heart failure: Rat coronary ligation model, Rat aortic banding, Dahl salt sensitive rats, Spontaneous Hypertensive Rat, and Spontaneous Hypertensive-Heart Failure Rats (SH-HF). Dog Models: Chronic rapid pacing, Volume overload and Coronary artery ligation and micro embolization. Rabbit models: Volume and pressure overload, Tachycardia pacing and Doxorubicin cardiomyopathy. Guinea pig model: Aortic banding. Syrian hamster model: Cardiomyopathic hamster. Transgenic mice model. Conclusion: Experimental models of CHF gives quick summary of most popular animal models, their characteristics, and their significance for new drug discovery for novel Anti- Congestive heart failure agents.

Keywords: New Drug Discovery of Anti-Congestive Heart Failure agents; In-vitro including rat, dog, rabbit, and guinea pig models; In-vivo including rat, dog, rabbit and guinea pig models; Transgenic mice model.

Introduction

Heart failure, also known as congestive heart failure (CHF), is a condition in which the heart cannot adequately pump blood to the body is other organs. This can be brought on by heart valve disease brought on by previous rheumatic fever, narrowed arteries that supply blood to the heart muscle, previous heart attacks, myocardial infarctions with scar tissue that interferes with the heart muscle's normal function, high blood pressure, cardiomyopathy, congenital heart defects, endocarditis, and/or myocarditis. Fatigue is a preliminary sign of congestive heart failure. Swelling (oedema) of the ankles, legs, or abdomen may be seen when CHF worsens. Moreover, fluid build-up in the lungs can result in shortness of breath, especially when lying flat and exercising. Fluid build-up in the liver and intestines may result in nausea, abdominal pain, and decreased appetite [1].

We have made significant progress in the previous ten years in both our knowledge and treatment of heart failure. Congestive heart failure (CHF) affects 1 to 2% of middle-aged and older adults, 2 to 3%

of patients over the age of 65, and 5 to 10% of patients over the age of 75 [2]. The baroreceptor reflex, the sympathetic nervous system, the kidney, the renin-angiotensin-aldosterone system, vasopressin, and the death of cardiac cells are just a few of the processes and organs that are thought to play a role in early heart failure, even though it is thought that the primary defect lies in the excitation-contraction coupling machinery of the heart [3-5]. Cardiac glycosides (digitalis), which boost cardiac output and change the heart's electrical processes, are a part of traditional CHF treatment. They boost cardiac contractility to balance out failure-related imbalances. Clinical studies have demonstrated that medication aimed at non-cardiac targets may be more effective than positive inotropic drugs in the long-term management of heart failure (cardiac glycosides). Diuretics, which affect the kidneys, have thus long been seen to be at least as effective for treating this illness as digitalis. Vasodilators and ACE inhibitors have become widely used over the past 20 years. Drugs that inhibit B-adrenoceptors are also used to treat CHF. Without a variety of animal models of heart failure and hypertrophy, each with specific benefits and drawbacks, advancements in our knowledge of pathogenesis and therapy of CHF would not have been conceivable. The species and manipulations used to produce CHF depend on a variety of elements, including the model's repeatability, accessibility, and ethical and financial implications.

In-Vitro Methods

Isolated Hamster Cardiomyopathic heart

The evaluation of cardiotonic medicines can be done on isolated Syrian hamster hearts. For the investigation, hamsters with cardiomyopathy in the 50-week age group were employed. As controls, normal Syrian hamsters of the same age are employed. Heparin (5 mg/kg) is administered intraperitoneally to the animals as a pre-treatment. Twenty minutes later, the heart is prepared using Langendorff's procedure, perfused with Ringer solution, and allowed to equilibrate in the isolated condition for 60 min at 32°C with a preload of 1.5 g. A force transducer attached to a polygraph records the force of contractions three times. A chronometer is used to measure heart rate. An electro flowmeter is used to calculate the coronary flow. The aortic cannula is used to provide test substances into the inflowing heart-Ringer solution.

The student t test is used to compare the contractile force and coronary flow in the hearts of the treated and sham control groups. The percentage improvement is determined, and the drug's effectiveness in boosting coronary flow and contractile force is assessed [6].

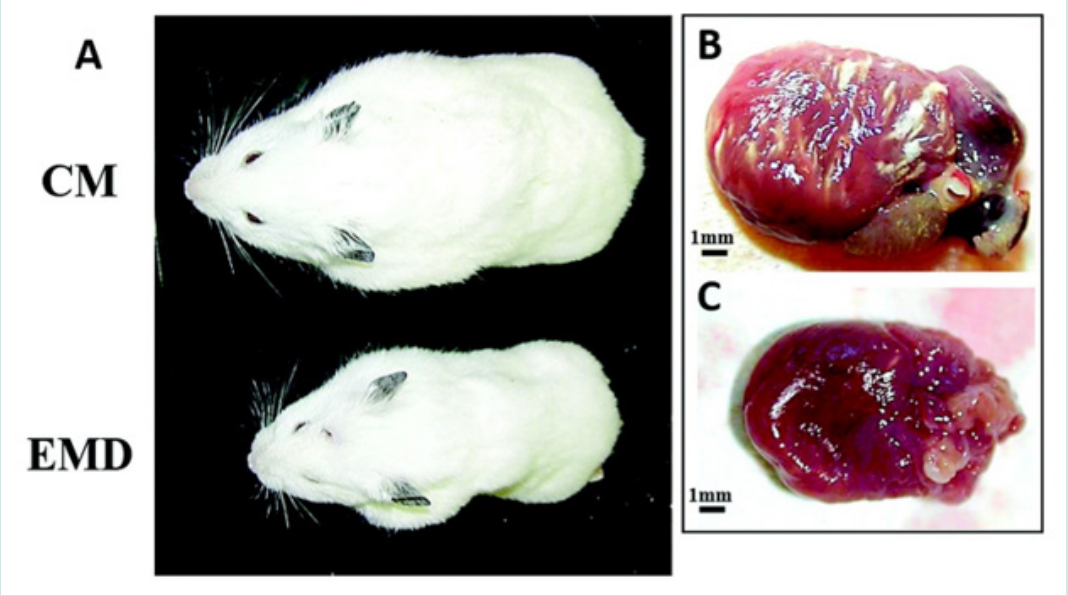

Figure 1: Dorsal photographs of hereditary cardiomyopathic (CM) hamsters (228 days old) of the UM-X7.1 strain (A) and their corresponding hearts (B and C) showing the effect of a preventive treatment (starting at the age of 30 days) for 198 days with a sodium–hydrogen exchanger-1 (NHE-1) inhibitor, EMD87580, on the development of body oedema as well as cardiac necrosis and hypertrophy.
(Ghassan Bkaily and Danielle Jacques. 2017. Na+–H+ exchanger and proton channel in heart failure associated with Becker and Duchenne muscular dystrophies. Canadian Journal of Physiology and Pharmacology. 95(10): 1213-1223. https://doi.org/10.1139/cjpp-2017-0265)

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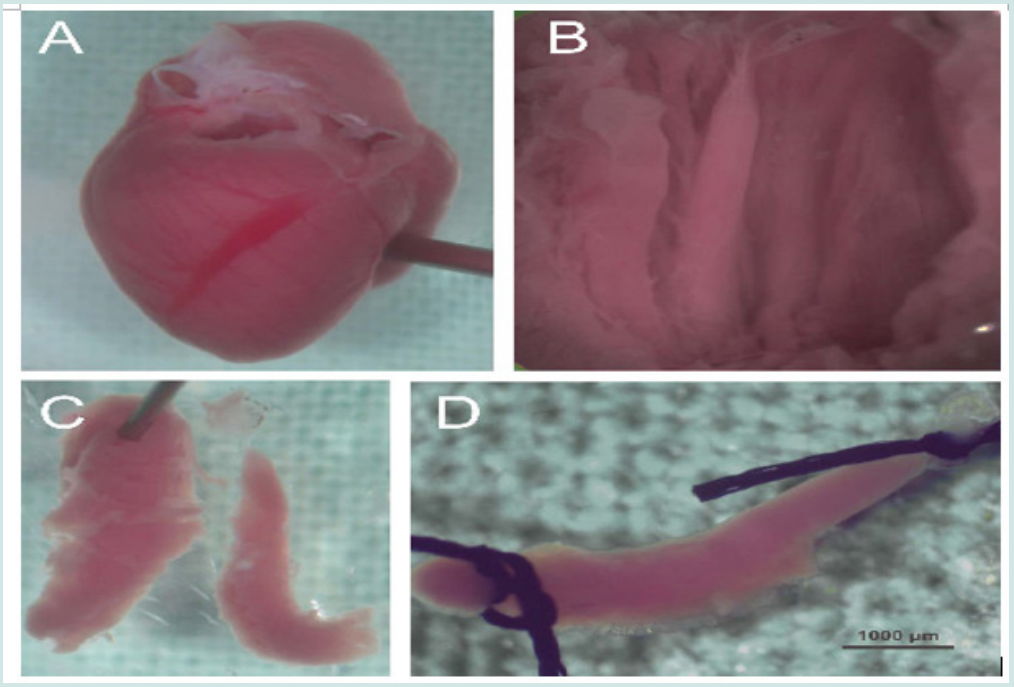
Isolated Rat Papillary Muscle

Catell and Gold have reported this procedure utilising rat capillary muscle [7]. Long-term electrical stimulation of isolated heart tissue decreases function. The force of contraction is restored by cardiac glycosides. Rats of any sex are put to sleep with ether. The heart is seen through a left thoracotomy. The right ventricular papillary muscle is isolated and fixed in a Ringer solution-containing organ bath that is kept at 37°C. The papillary muscle is attached to a strain gauge at one end and to the muscle at the other. Muscle contractions are monitored on a polygraph while an electrical stimulation of 4-6 V is administered to it at a rate of 30/min. After receiving electrical stimulation for one hour, the muscle contractions start to decrease. To regain the contractile force, cardiac glycosides are now introduced to the bath. The common glycoside, ouabain, is added at a dose of 300 ng/ml. Assessment is based on the glycoside-induced increase in contractile force. To compare various groups, contractile force is computed as a percentage of predose level. Figure 2: Key steps of the papillary muscle preparation. (A) Dissection of both atria. (B) View on the left ventricular anterior papillary muscle. (C) Dissection of the papillary muscle from the ventricular wall. (D) Attachment of two silk threads before the fixation in the organ bath chamber. (Uhl, S., Freichel, M., Mathar, I. Contractility Measurements on Isolated Papillary Muscles for the Investigation of Cardiac Inotropy in Mice. J. Vis. Exp. (103), e53076 URL: http://www.jove.com/video/53076 DOI: doi: 10.3791/53076.)



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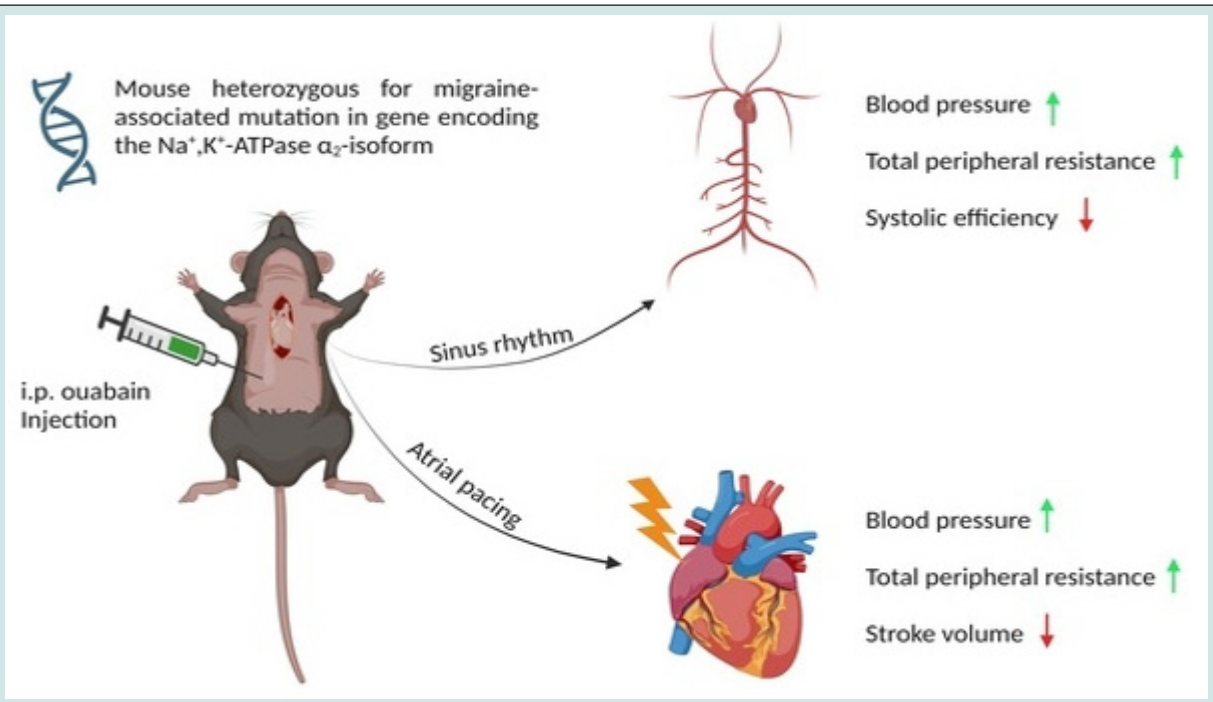
Ouabain binding

The cardiac glycosides exhibit the binding kinetics, association process, equilibrium binding, and dissociation process at the outbid receptor. Myocytes are then extracted from rat hearts by digesting collagen after coronary perfusion. Myocytes sarcolemma are produced from these separated membrane components. In 10 ml of binding medium held at 37°C for 10 min, radioactive ouabain PH) with specific radioactivity of 20 Ci/mmol is treated with ligands. The ingredients in binding- Imm MgCl, 50 mm Tris HCI, and 1 mm inorganic phosphate make up the medium (pH 7.4). Once temperature equilibrium has been reached in the presence of 10 or 100 nM [H] ouabain, 200 g of membrane preparation are introduced to start the reaction. At various points, 45 ml aliquots are taken out and filtered (Association process). Once temperature equilibrium has been reached, 40 ug of membrane are applied in the presence of an increased concentration of 'H ouabain ranging from 10 nm to 3 ums. After 30 minutes, an aliquot of 4.5 ml is taken out and filtered: equilibrium binding. After reaching temperature equilibrium, 10 ml of prewarmed Mg and P-Tris-HCl solution are added, along with 0.2 mm of unlabeled ouabain, to start the dissociation process. At various points, aliquots of 0.9 ml are taken out and filtered (dissociation process) [8]. All aliquots are processed under vacuum using Millipore filters (0.45 pm) and three ice-cold buffer rinses. Radioactivity bound to filters is identified

through specific binding measurements. Across different groups, Scat chard plots are used to examine the outcomes of equilibrium binding and compute the kinetics of the association and dissociation processes. Figure 3: Augmented Ouabain-Induced Vascular Response Reduces Cardiac Efficiency in Mice with Migraine-Associated Mutation in the Na+, K+-ATPase α2-Isoform. (Rajanathan, R.; Pedersen, T.M.; Guldbrandsen, H.O.; Olesen, L.F.; Thomsen, M.B.; Bøtker, H.E.; Matchkov, V.V. Augmented Ouabain-Induced Vascular Response Reduces Cardiac Efficiency in Mice with Migraine-Associated Mutation in the Na+, K+-ATPase α2-Isoform. Biomedicines, 2023, 11, 344. https://doi.org/10.3390/biomedicines11020344)



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In-Vivo Models

Rat Models of heart failure

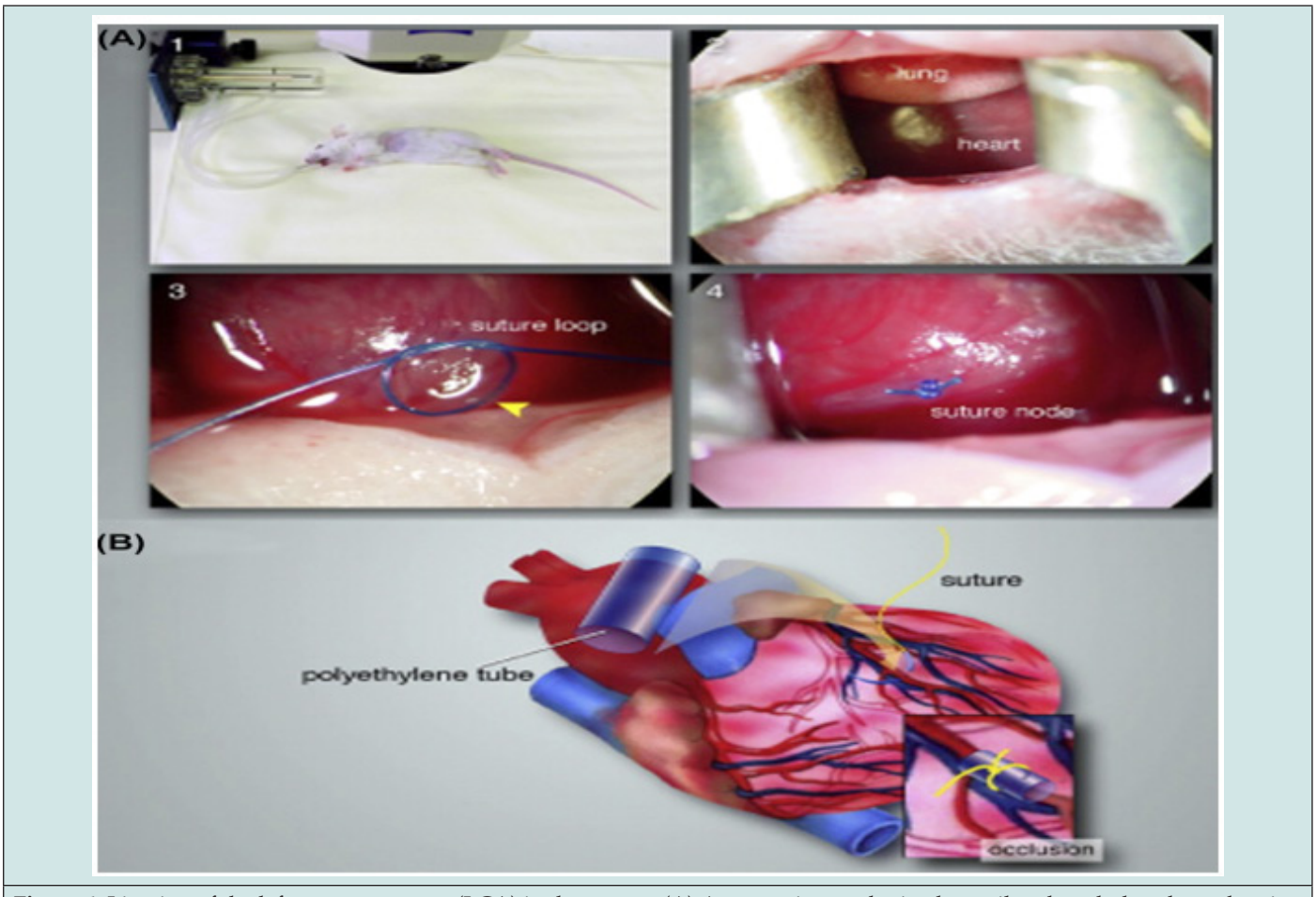
Rat models are reasonably priced, and since their gestation periods are brief, a large sample size may be created quickly. To research long-term pharmacological therapies, including long-term survival trials, rat models have been employed extensively [9,10]. Yet, there are significant drawbacks to using rat models for myocardial function that differ from that of the human heart. The action potential of the rat myocardium is extremely brief and typically does not have a plateau phase. The sarcoplasmic reticulum calcium pump predominates in the removal of calcium from the cytosol, while Na/Ca exchanger activity is less significant. A shift towards the B-myosin isoform and alterations in hemodynamic load or hormone levels occur when the a-myosin heavy chain isoform predominates in normal rat myocardium. The force-frequency ratio is inverse, and the human resting heart rate is five times that of an animal [11].

Rat coronary ligation model

A common rat model of heart failure is myocardial infarction after coronary artery closure in Sprague-Dawley rats. Chronic myocardial ischemia may lead to cardiac failure if the left coronary artery is not totally blocked [12]. Full blockage of the left coronary cause's myocardial infarctions of various sizes, with heart failure developing in some animals with big infarcts after 3-6 weeks. Loss of myocardium is correlated with a reduction in left ventricular function. Left ventricular enlargement, diminished systolic function, and elevated filling pressures are all indicators of failure. Phenobarbitone 200 mg/kg is administered to 250–300 g male Sprague–Dawley rats to put them to sleep. A cannula is inserted into the animal's trachea, and artificial breathing is used to keep it alive. In addition to the left anterior descending carotid artery (LAD) being isolated, the chest cavity is seen. After the chest cavity is stitched back together and a ligature is placed around the LAD, the animal is kept on a diet of unlimited amounts of food and liquids. The carotid artery and jugular vein are cannulated after 4 weeks to measure blood pressure and to provide test substances. The thoracic cavity is then accessed. Blood pressure readings include filling pressure, systolic, diastolic, and mean. Animals are killed after the hemodynamic parameters are measured, and the isolated hearts are used to research the calcium channel and sarcoplasmic reticulum ATPase and protein levels. The advancement of left ventricular dysfunc-

tion and cardiac failure in the control group is linked to neurohumoral activation resembling that found in CHF patients. Alterations in calcium transients are linked to decreased myocardial function. L-type calcium channel density and SR-Ca ATPase and protein levels continuously decline as congestive heart failure becomes more severe. Based on the above-mentioned factors, comparisons between the test group and the control group are made. Although this model may have a high initial death rate and typically induce mild heart failure, it appears to be particularly helpful for long-term studies of pharmacological interventions on neuro-hormonal activation [13].

Figure 4: Ligation of the left coronary artery (LCA) in the mouse. (A) A mouse is anesthetized, ventilated, and placed on a heating mat. A left-sided thoracotomy is performed, and the ribs retracted, revealing the lung and heart. Proline is used to suture the left coronary artery (arrowhead marks suture). After suturing, the area of myocardium downstream of the blockage immediately becomes pale. (B) To allow release of the suture, and therefore reperfusion of the ischemic myocardium, the suture is placed around the LCA and a small length of polypropylene tubing, allowing the suture to be cut and removed without damaging the myocardium. Source: adapted from Klocke et al., 2007. (Ross A. Breckenridge, in Animal Models for the Study of Human Disease, Animal Models of Myocardial Disease, Chapter 7, 2013. 145-171. https://doi.org/10.1016/B978-0-12-415894-8.00007-5)



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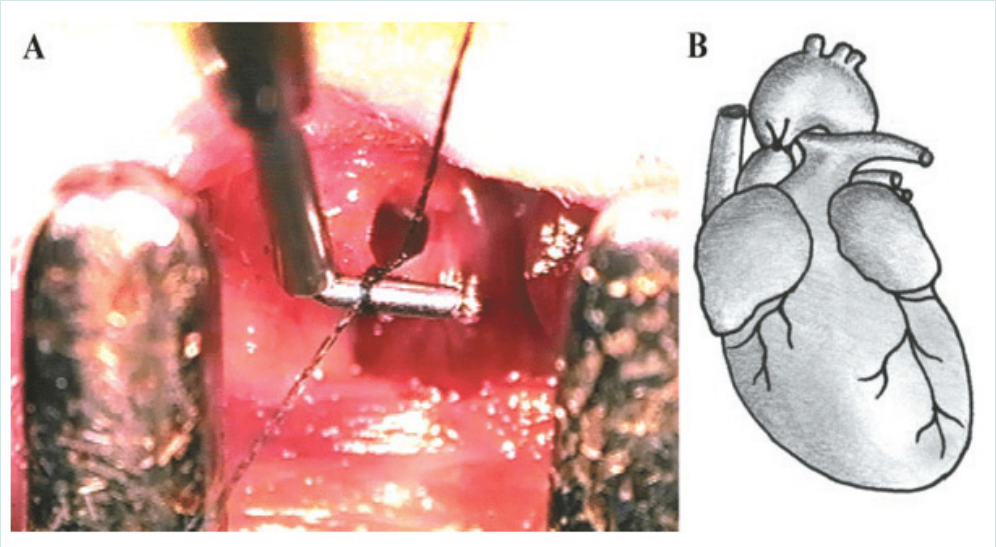
Rat aortic banding

Within a few months, fractions of rats with restricted aortic blood flow develop congestive heart failure in addition to hypertension. Ventricular ACE activity may return to normal values over a period of several weeks, which may be related to normalization of wall stress with increasing heart hypertrophy 12 hours before surgery, Sprague-Dawley rats (250-280 g) are fasted [14]. Hexobarbitone, 200 mg/kg, is administered intraperitoneally to anaesthetize animals. The

abdomen is seen through an incision made parallel to the Linea alba. The connective tissue is removed from the aorta. The aorta and cannula are connected after a cannula is positioned longitudinally to it. The aortic lumen is left patent once the cannula is removed. Clipping is used to seal the skin. Animals in the test group receive medication for 6 weeks while those in the sham-operated controls do not have bands applied. Heart failure is seen to develop in these animals after 4-6 weeks. The carotid artery is cannulated and hexobarbital anesthesia (200 mg/kg, intraperitoneally) is administered at the conclusion of the experimental period. Animals are killed and their hearts are completely removed and total cardaic mass is determined. Increased levels of atrial natriuretic factor and myosin heavy chain mRNA are related to heart failure. The catecholamine levels are normal during compensatory hypertrophy; the local myocardial renin-angiotensin system is activated, which may be crucial for the onset of heart failure [15]. Both the test group and the fictitious control group are used in the analysis of the above-mentioned factors. Through the left coronary artery, blood pressure and heart rate are measured at the conclusion of the trial. In addition, the weight of the left and right ventricles as well as the overall cardiac mass of treated rats are compared to sham-operated controls. This model appears to be well adapted for researching the change from myocardial hypertrophy to failure. Figure 5 Ascending aortic banding. A: 7-0 silk suture is tied around the aorta and 25-gauge needle. B: position of the suture on the aorta. (Tarnavski O, McMullen JR, Schinke M, Nie Q, Kong S, Izumo S. Mouse cardiac surgery: comprehensive techniques for the generation of mouse models of human diseases and their application for genomic studies. Physiol Genomics. 2004 Feb 13; 16(3):349-60. PMID: 14679301. Doi: 10.1152/physiolgenomics.00041.2003.)



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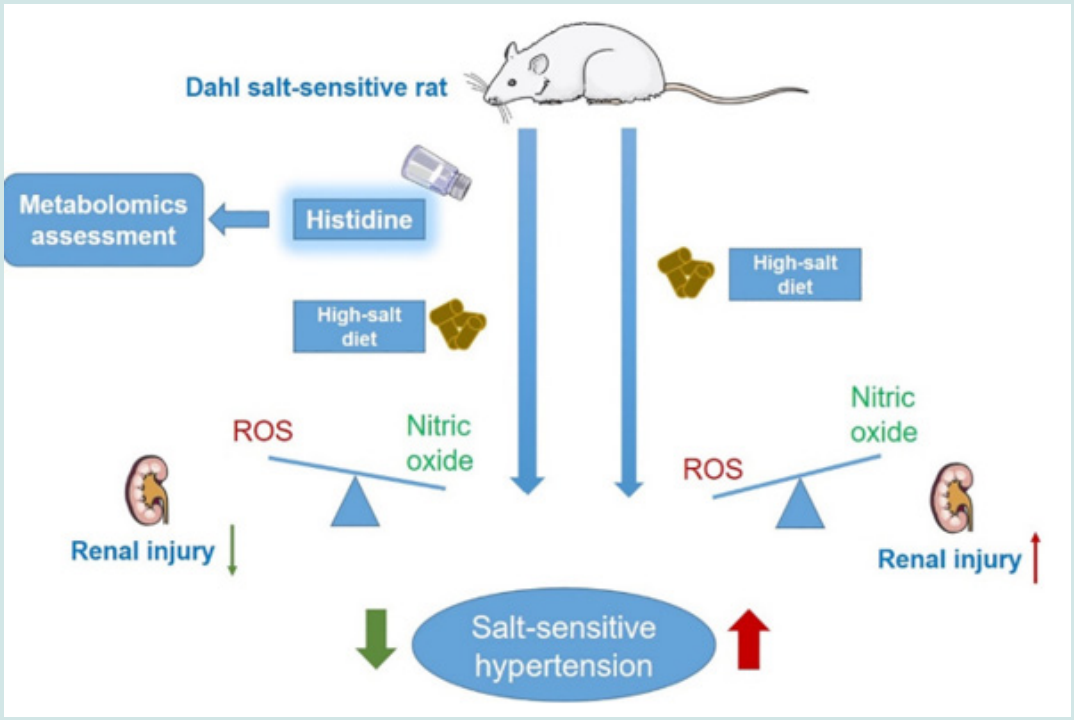
Dahl salt sensitive rats

This model is ideal for researching the change from compensatory hypertrophy to failure [16]. After being fed a diet heavy in salt, this strain of rats develops systemic hypertension. The study uses Sprague-Dawley rats weighing 250–300 g. A 1% NaCl saline solution is used in place of drinking water. In a lab setting, salt and a regular food are combined to create a high Dahl salt diet. Animals are given an unlimited supply of the prepared meal and 1% NaCl solution. For one month, the medication is given orally to the rats in the treatment group. The test group's animals and the sham control group's animals are both slaughtered at the end of the study period. Their hearts are removed, and the weights of the left and right ventricles, as well as the total cardiac mass, are weighed and compared. The sham control group animals show concentric left ventricular hypertrophy at 8 weeks, followed by noticeable left ventricular dilatation and overt clinical heart failure at 15-20 weeks, according to observations. In a short time, a failing heart passes away. It is investigated whether the test substance can undo these modifications [17]. Figure 6 Protective effect of oral histidine on hypertension in dahl salt-sensitive rats induced by high-salt diet. (Gillis EE, Williams JM, Garrett MR, Mooney JN, Sasser JM. The Dahl salt-sensitive rat is a spontaneous model of superimposed preeclampsia. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2015 Jul 1; 309(1): R62-70. PMID: 25904684; PMCID: PMC4491533. DOI: 10.1152/ajpregu.00377.2014)



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Spontaneous Hypertensive Rat

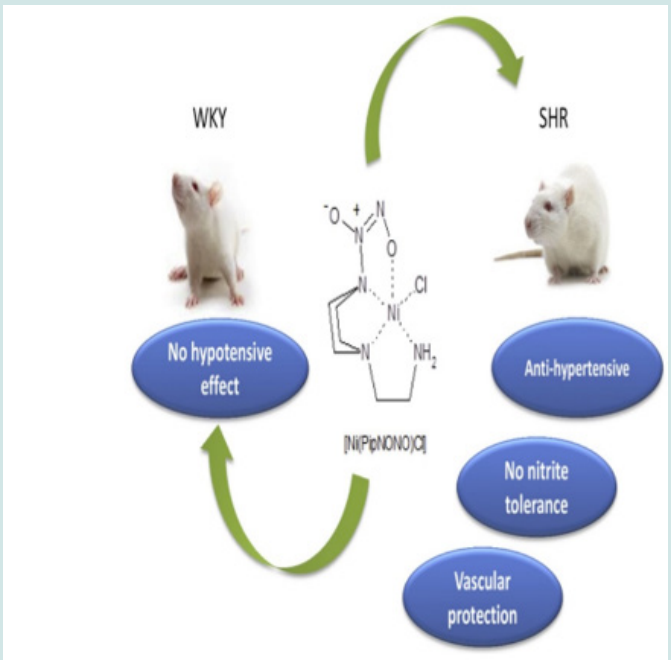


Figure 7: Anti-hypertensive property of a nickel-piperazine/no donor in spontaneously hypertensive rats
(Stokes KY, Cooper D, Tailor A, Granger DN. Hypercholesterolemia promotes inflammation and microvascular dysfunction: role of nitric oxide and superoxide. Free Radical Biology and Medicine. 2002 Oct 15; 33(8):1026-36. PMID: 12374614. DOI: 10.1016/s0891-5849(02)01015-8)

A well-known model of hereditary hypertension is the spontaneously hypertensive rat, in which ventricular pump function is still present at 1 year of age [18]. After 18 to 24 months, heart failure manifests as increasing fibrosis and decreased myocardial function. In this model, the change from compensatory hypertrophy to failure is not accompanied by a decrease in the mRNA of the sarcoplasmic reticulum calcium pump, despite the observation of altered calcium cycling. Significant changes in the expression of genes encoding extracellular matrix are linked to the transition to failure [19]. Apoptosis may also be a factor in the decline in myocyte mass that occurs along with the transition from stable compensation to heart failure, according to the observation of an increased number of apoptotic myocytes. Two groups of animals have been established. Drugs are given orally to test group animals for a month, but sham control group animals do not get any pharmacological treatment. Following the conclusion of the experiment, the animals are killed, and the hearts are processed to estimate the number of apoptotic cells, sarcoplasmic reticulum calcium pump mRNA levels, and expression of genes encoding for extracellular matrix, with the results being compared. Figure 7: Anti-hypertensive property of a nickel-piperazine/no donor in spontaneously hypertensive rats (Stokes KY, Cooper D, Tailor A, Granger DN. Hypercholesterolemia promotes inflammation and microvascular dysfunction: role of nitric oxide and superoxide. Free Radical Biology and Medicine. 2002 Oct 15; 33(8):1026-36. PMID: 12374614. DOI: 10.1016/s0891-5849(02)01015-8).

Spontaneous Hypertensive-Heart Failure Rats (SH-HF)

Rats with spontaneous hypertension who experience failure before the age of 18 months are utilised to research how CHF develops. These rats have a faulty leptin receptor (SH-HF/Mcc-facp) encoded by the facp gene (corpulent a). As people get older, their levels of renin plasma activity, atrial natriuretic peptide (ANP), and aldosterone rise as well. Renin plasma activity also independently correlates to cardiac hypertrophy.

Animals are split into two categories. Group 1 is the test drug group (had the medicine orally for one month), and Group 2 is the fictitious control group (untreated). Following the experiment, comparisons are made between the two groups based on their ryanodine receptor density, aldosterone and ANP levels, and plasma renin activity. Calcium uptake in the sarcoplasmic reticulum and endothelial NOS activity. A greater negative force frequency connection is visible in the hearts of SH-HF rats than in control rats, which is an interesting finding. A recent experimental trial in SH-HF rats revealed normal sarcoplasmic reticulum calcium uptake, ryanodine receptor activity, and calcium current density. The likelihood of a spark was shown to be inversely correlated with calcium current density, indicating that the calcium influx was less effective at causing SR calcium release. These alterations were thought to be associated with spatial remodelling between ryanodine receptors and L-type calcium channels [20,21]. Figure 8 Pathomorphological, pathophysiological, and clinical patterns of hypertensive heart failure disease, LV-Left ventricle, LA-Left atrium. (Nemtsova, V.; Vischer, A.S.; Burkard, T. Hypertensive Heart Disease: A Narrative Review Series—Part 1: Pathophysiology and Microstructural Changes. J. Clin. Med. 2023, 12(7), 2606. PMID: 37048689. PMCID: PMC10094934. https://doi.org/10.3390/jcm12072606).

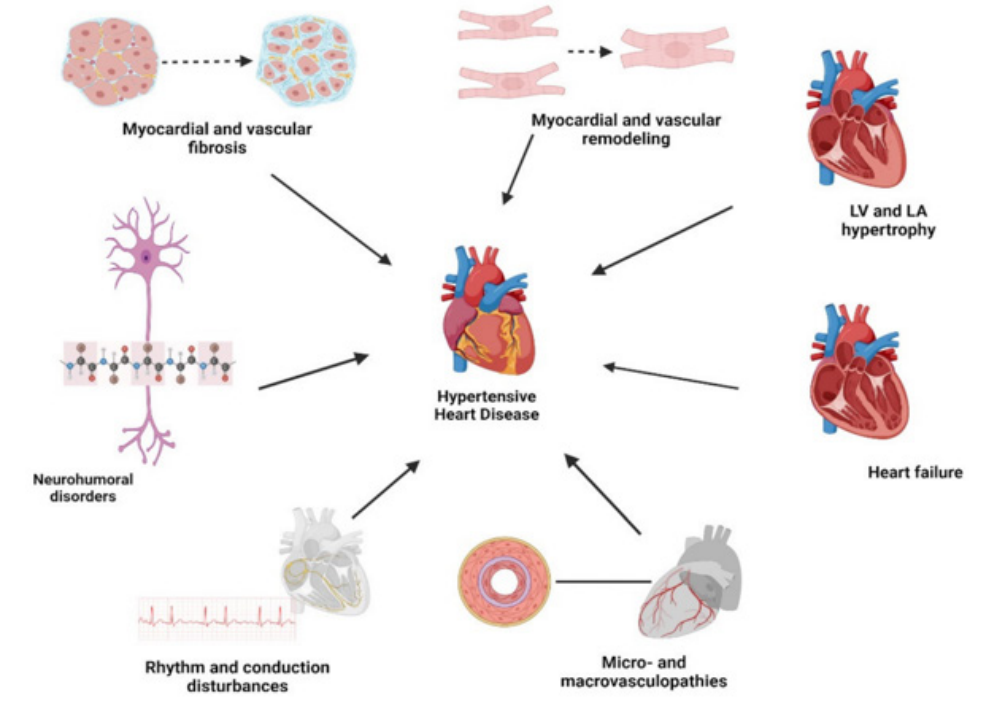


Figure 8: Pathomorphological, pathophysiological, and clinical patterns of hypertensive heart failure disease, LV-Left ventricle, LA-Left atrium.
(Nemtsova, V.; Vischer, A.S.; Burkard, T. Hypertensive Heart Disease: A Narrative Review Series—Part 1: Pathophysiology and Microstructural Changes. J. Clin. Med. 2023, 12(7), 2606. PMID: 37048689. PMCID: PMC10094934. https://doi.org/10.3390/jcm12072606)

Dog Models of Heart Failure

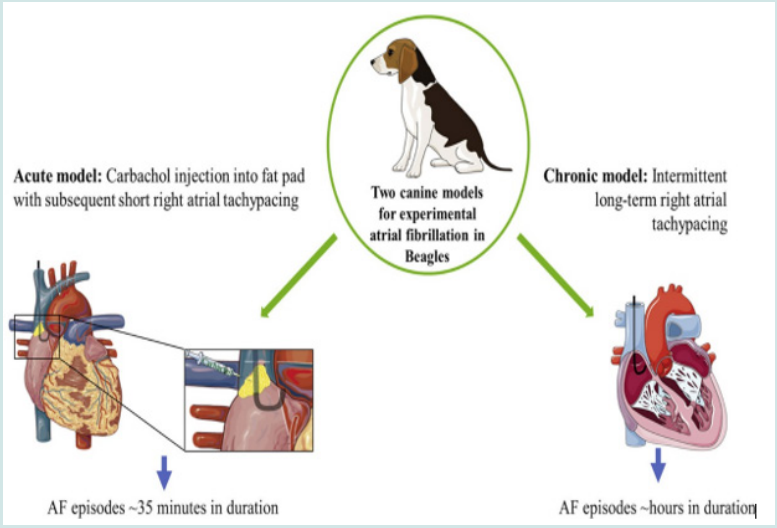
Dog as an animal model of heart failure allows the study of left ventricular function and volumes more accurately than rodent models. They allow better chronic instrumentation. In dog like human myocardium, the B-myosin heavy chain isoform predominates and excitation contraction coupling processes seem to be like the human myocardium. The force frequency relationship, the slope of the end-systolic pressure-volume relation is positive in automatically intact awake dogs as well as during autonomic blockade. However, dog models are costly and require substantial resources with respect to housing and care.

Chronic rapid pacing

Within a few weeks, the CHF condition is brought on in previously healthy dogs by prolonged rapid pacing with heart rates above 200 beats per minute. Pentobarbitone (30 mg/kg) is administered intraperitoneally to adult male dogs (18–25 kg) to make them unconscious. The animal is kept alive with artificial breathing (20–24 breaths per minute). A 3 to 4 cm long thoracotomy is used to open the chest cavity and expose the heart. The left ventricular apex is connected to a ventricular pacing lead. The pacemaker is set to pace for two to four weeks at 240-260 beats per minute. After the surgery, the heart is repositioned in the chest cavity, the costal ribs are closed, and the musculus pectoralis is placed over the undated portion of the thorax by exerting pressure on both sides of the thorax. After 4 hours of antibiotic emulsion application, the skin wound has healed. Animals are divided into two groups: the treatment group (which receives the test drug therapy) and the sham control group (which receives saline treatment). In the sham-control group, severe heart failure starts to manifest after four weeks and lasts for up to ten weeks. The bulk of research shows that prolonged fast tachycardia causes ventricular chamber dilatation to proceed over a 3 to 4 week timeframe. Over the course of 14 days, the test medications are given intramuscularly or subcutaneously (treatment group).

Ejection fraction and diastolic suction both significantly decline in heart failure, which is followed by decreased cardiac output and elevated systemic vascular resistance [22]. When electrical pacing is halted, heart failure is reversible according to clinical hemodynamic and neurohumoral analyses. This model's precise aetiology is still unknown. There are time-dependent changes in neurohumoral adiation, early sympathetic activation, an increase in plasma catecholamine levels, and loss of parasympathetic tone, which are like human heart failure. Moreover, the development of left ventricular dysfunction is accompanied by an increase in plasma ANP levels. Renin-angiotensin systemic activation is associated with progressive pump failure. Furthermore, endothelial dysfunction with nitric oxide-based coronary vasodilation has been seen in patients with heart failure. Ejection fraction, cardiac output, and systemic vascular resistance changes are used to compare the treatment group to the sham control group. To examine the possible Cardioprotective effects of test medications, additional plasma catecholamine, ANP levels, and renin activity are also measured. Pigs and sheep have also used the tachycardia pacing approach and results similar to those in dogs in terms of clinical hemodynamic and neurohumoral alterations have been seen. This model appears to be quite useful for examining peripheral circulation changes and neurohumoral mechanisms that closely mirror human heart failure [23].

In a related model of CHF, several Tran myocardial direct current shocks delivered by a catheter into the left ventricular chamber of sedated dogs cause left ventricle hypertrophy and dilatation, a decrease in ejection fraction, and a reduction in cardiac output over the course of four months. Increased plasma catecholamine levels are linked to this, while plasma renin activity remains unaffected [24]. Figure 9 Identification of two preclinical canine models of atrial fibrillation to facilitate drug discovery. (Till Freudenberger, Beate Kranz, Waldemar Lehmann, Katja Schäfer, Klaus Münter, Kichang Lee, Patrick T. Ellinor, William J. Hucker. Identification of two preclinical canine models of atrial fibrillation to facilitate drug discovery. Heart Rhythm 18(4), April 2021, 632-640 https://doi.org/10.1016/j.hrthm.2020.12.015).



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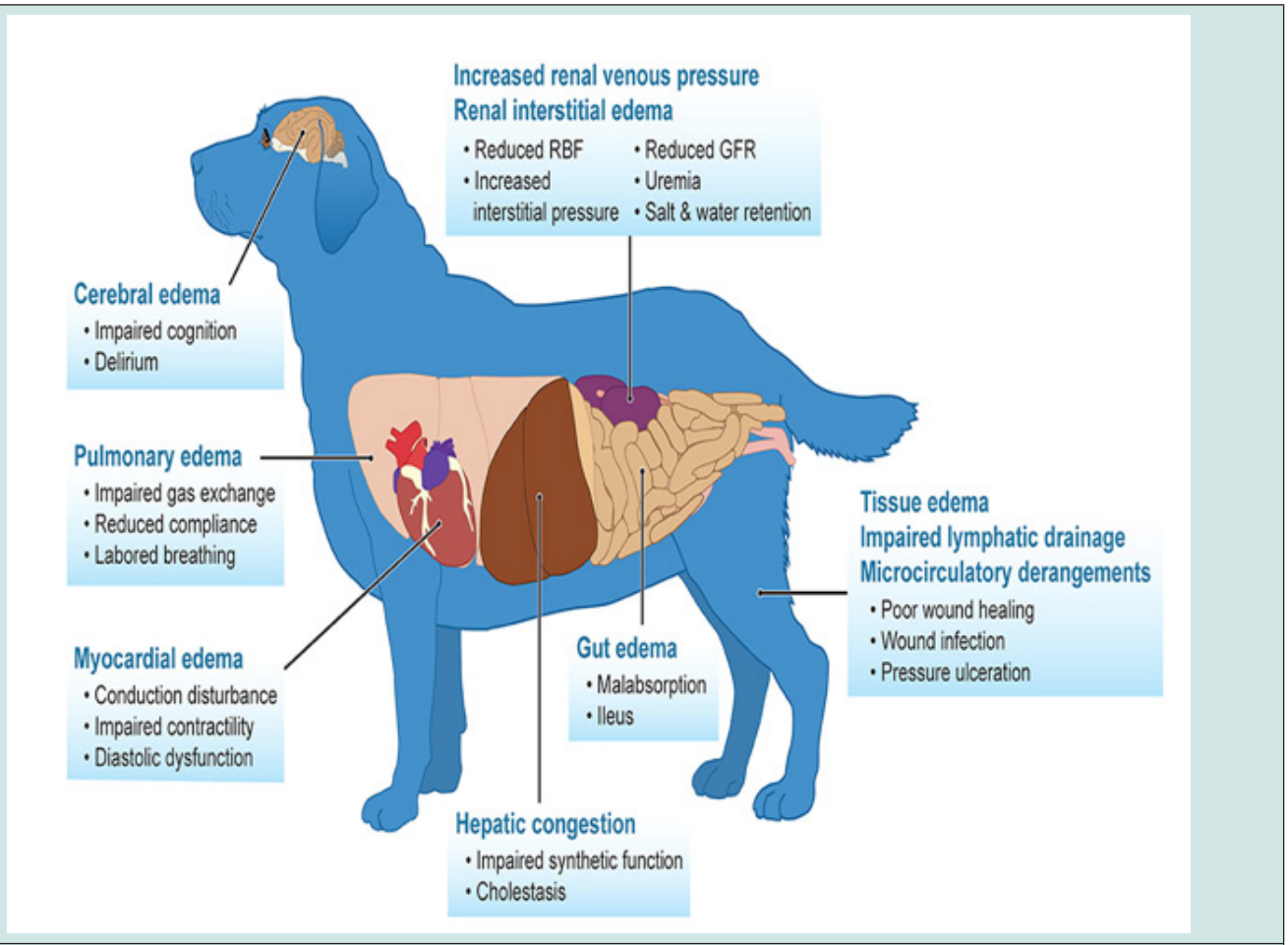
Volume overload

Heart failure could develop because of persistent volume overload. To improve venous flow, an end-to-side anastomosis between the femoral vein and artery is established to create an arteriovenous fistula in dogs. Alternatively, the mitral valve can be destroyed in closed-chest dogs using arthroscopically placed grasping forceps. In this model, clinical heart failure manifests as left ventricular hypertrophy, dilatation, and development within 3 months [25]. Pentobarbitone (30 mg/kg) is administered intraperitoneally to anaesthetize dogs (12–15 kg), who are then kept on artificial respiration (20–24 strokes/min). The heart is exposed during a thoracotomy. By rupturing the mitral chordae or leaflets with an arterially inserted foreceps, chronic experimental mitral regurgitation is created in closed chest dop. The costal ribs are stitched together, and the heart is returned to the chest cavity after the operation. It is possible to expel air from the thorax by exerting pressure on both sides of it. The skin wound is sealed after the application of an antibiotic emulsion. Two treatment groups (test drug treated) and a sham control group are used to group the animals (saline treated group). In the treatment group, the test medications are provided subcutaneously or intramuscularly over the course of 14 days, while in the sham control group, severe heart failure starts to develop after four weeks and can last for up to ten weeks groups. Dogs in the sham-control group showed neurohumoral activity, including local renin-angiotensin system activation, which is typically linked to worse cardiac function. After the experiment is over, the animals are killed, their hearts are removed, and measurements of the cardiac mass and weight of the left and right ventricles are made. Comparisons are conducted between the treatment group and a phony control group (animals not receiving treatment). Using the animal, researchers have examined how chronic ß-adrenoreceptors blockage affects myocytes and left ventricular function, both of which markedly improve with treatment [26]. Figure 10 Effects of IV fluids in dogs and cats with kidney failure (Henik RA, Dolson MK, Wenholz LJ. How to obtain a blood pressure measurement. Clinical Techniques in Small Animal Practice. 2005 Aug 1; 20(3):144-50. doi: 10.1053/j.ctsap.2005.05.005).



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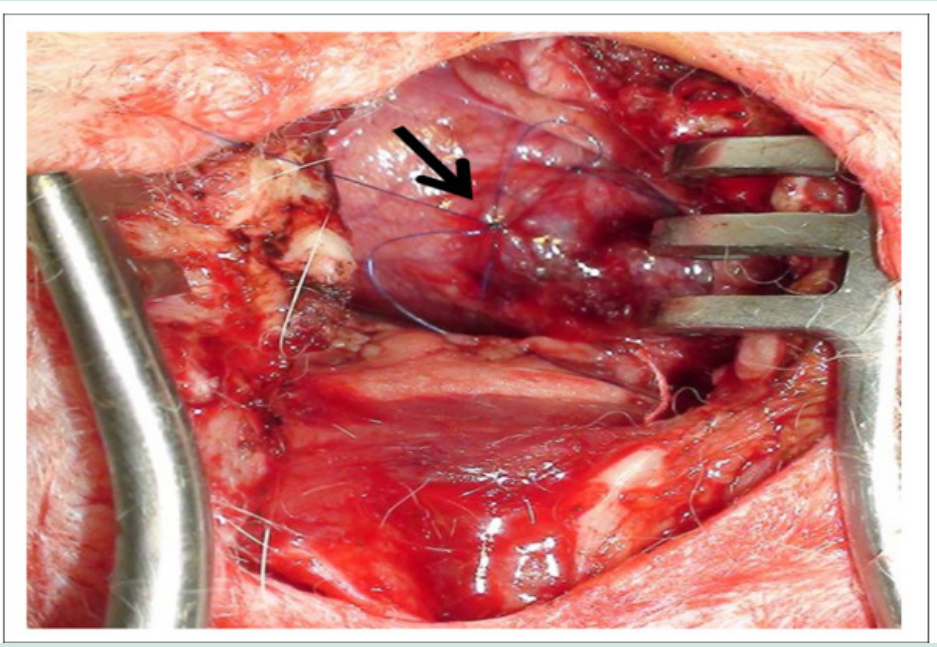
Coronary artery ligation and micro embolization

Myocardial infarction and CHF have been induced in dogs using coronary artery ligation and micro embolization. 30 kg dogs of either sex are given an intravenous bolus injection of 35–40 mg/kg Pentobarbitone to put them to sleep. Artificial respiration is used to keep animals alive. The carotid and femoral arteries have been cannulated. Right femoral artery transducer is used to measure peripheral systolic, diastolic, and mean blood pressure. To measure left ventricular pressure, a microtip catheter was placed into the left carotid artery. By employing the thermodilution technique with a cardiac index computer, it is possible to measure the systolic, diastolic, mean pulmonary capillary pressure, and cardiac output. The pericardium is opened, and the heart is made visible through a thoracotomy between the fourth and fifth intercostal spaces. Using the angiography catheter, polystearyl microsphere is injected into the left atrium. A 10 ml (1 mg/ml) microsphere is administered first, followed by a 5 ml bolus around 5 minutes later. Stepwise rise of left ventricular end diastolic pressure is caused by the microsphere injection (LVEDP). When LVEDP rises to 16–18 mm Hg or heart rate reaches 200 beats per minute, embolism is halted. The test material is administered via continuous infusion or intravenous bolus injections. At various time intervals, recordings are taken before and after embolization and the delivery of test substance [27,28].

Figure 11 Coronary artery ligation and micro embolization (Katsanos K, Mitsos S, Koletsis E, Bravou V, Karnabatidis D, Kolonitsiou F, Diamantopoulos A, Dougenis D, Siablis D. Trans auricular embolization of the rabbit coronary artery for experimental myocardial infarction: comparison of a minimally invasive closed-chest model with open-chest surgery. J Cardiothoracic Surg. 2012 Feb 13; 7:16. PMID: 22330077; PMCID: PMC3307024. Doi: 10.1186/1749-8090-7-16.)



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Rabbit models of heart failure

Models of rabbits cost less than those of dogs. However, pet rabbit myocardial models that consistently function have intriguing parallels to the human heart. In adult animals, the f-myosin heavy chain isoform predominates. An estimated 30% of the calcium comes from the Na/Ca exchanger and 70% from the sarcoplasmic reticulum. Positive force-frequency relationships exist.

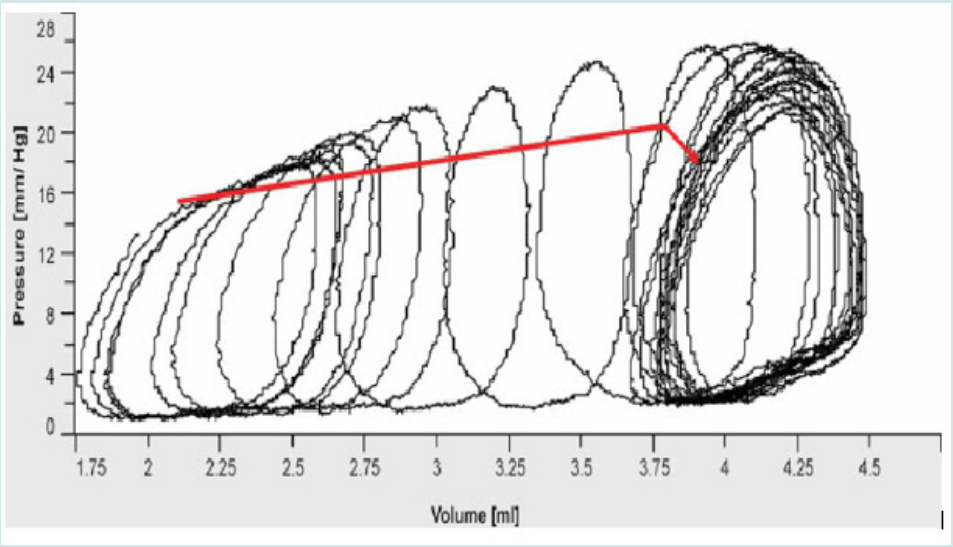
Volume and pressure overload

Rabbits are subjected to volume overload, pressure overload, or a combination of the two. In rabbits, aortic valve perforation caused chronic severe aortic regurgitation that resulted in left ventricular hypertrophy, systolic dysfunction, and heart failure after many months. Pentobarbitone sodium (35 mg/kg) is intraperitoneally used to anaesthetize rabbits. The animals' tracheas are cannulated, and they are kept on an artificial respiration system. One cannulates the carotid artery. The chest cavity is opened during a left thoracotomy, exposing the heart. A catheter inserted through the carotid artery damages the aortic valve, resulting in aortic insufficiency. An antibiotic is administered when the chest cavity is sutured back together to avoid infection. A PVC clamp is used to perform aortic constriction immediately below the diaphragm after 14 days. When aortic regurgitation and

aortic constriction coexist, heart failure occurs more frequently and with a quicker onset. Two sets of animals are used: the test drug-treated group and the sham control group (saline treated group). In the treatment group, test medications are given subcutaneously or intraperitoneally for two weeks.

In the sham-control group, heart failure appears roughly 4 weeks following the original surgery. Similar to human changes, it is connected to changes in the -adrenoceptor system. Moreover, this model exhibits an inversion of the force-frequency relation and a change in post-rest potentiation that closely parallels the conditions in the human heart. Intriguingly, failing animals have much higher protein and mRNA levels of the Na/Ca exchanger than nonfailing animals, yet there are no appreciable changes in the levels of sarcoplasmic reticulum Ca ATPase. The above-mentioned neurohumoral parameters, cardiac mass, and left and right ventricular weight are examined in the drug-treated and sham-control groups when the experimental protocol is complete [29]. The ability of the test group to reverse these changes is studied. This model is particularly adapted to research changes in excitation contraction coupling throughout the transition from compensatory hypertrophy to failure because it closely matches changes in cardiac function seen in the end-stage failing human myocardium.

Figure 12 Representative set of pressure-volume loops of the RV recorded in an adult rabbit during incremental pulmonary artery constriction. RV systolic pressure and RV elastance increased but failed to increase above 2-fold of the baseline value. As failure ensued with severe PA constriction, RV systolic pressure and elastance decreased (arrow) and RV end diastolic pressure increased.



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(Apitz, Christian & Honjo, Osami & Friedberg, Mark & Assad, Renato & Arsdell, Glen & Humpl, Tilman & Redington, Andrew. (2012). Beneficial Effects of Vasopressors on Right Ventricular Function in Experimental Acute Right Ventricular Failure in a Rabbit Model. The Thoracic and cardiovascular surgeon. 60. 17-23. Doi: 10.1055/s-0031-1298058.)

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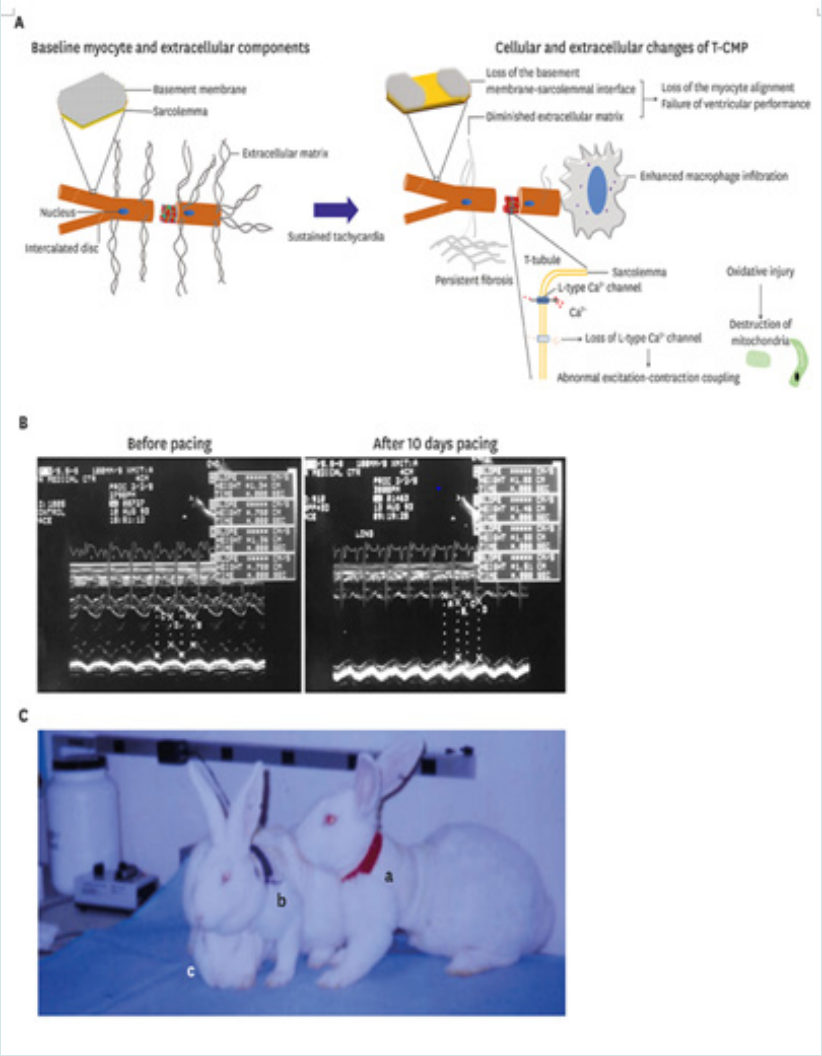
Tachycardia pacing

Over the course of many weeks, myocardial depression as well as hemodynamic and neurohumoral indications of heart failure in rabbits were induced by chronic fast pacing at rates between 350 and 400 beats per minute [30]. Pentobarbitone sodium (35 mg/kg) is intraperitoneally used to anaesthetize rabbits. The animal's trachea is cannulated, and they are kept on artificial breathing. A 3 to 4 cm long thoracotomy is performed to expose the heart after the thoracic cavity has been opened. The left ventricular apex receives a ventricle pacing lead, and the pacemaker is set to beat at 350 to 400 beats per minute for 2 to 4 weeks. After the operation, the intercostal ribs are closed, the air from the thorax is removed, and pressure is applied to both sides while the heart is placed back in the chest cavity. The wound is stitched up after applying an antibiotic emulsion. Heart failure sets in for the animals after 4-6 weeks. Animals in one experimental group receive the test substance subcutaneously or intraperitoneally for two weeks, while those in the other experimental group receive saline as a treatment (sham-control group). Both groups of animals undergo additional surgery when the study period is over. Blood pressure is measured by cannulating the carotid artery. Systolic, diastolic, mean blind pressure, and heart rate are all hemodynamic parameters that are assessed. The animals are subsequently killed, and the weight and processing of their hearts is done to determine the plasma renin activity.

Hemodynamic parameters and plasma renin act are used to compare the test group and sham control group. The force frequency relation is drastically depressed and inverted in the sham-control group (untreated group) at higher stimulation rates. This is comparable to how the force-frequency relation changes when human hearts fail. No left ventricular hypertrophy appears to occur in the rabbit model, as was seen in the tachycardia pacing dog failure model. Figure13 (A) Changes in cellular level in T-CMP. (B and C) Echocardiographic and gross change in pacing induced HF animal model. (A) Following sustained tachycardia, intracellular and extracellular remodelling leads to LV remodelling and worsening contractility. Decrease in L-type Ca2+ channel causes abnormal excitation-contraction coupling. Myocardial fibrosis persists even after recovery of LV function. (B) Echography in animal with pacing-induced HF (from Ryu et al., Ross et al.). (C) Gross change in pacing-induced heart failure in animal (from Ryu et al., Ross et al.)): (a) normal rabbit before pacing, (b) low cardiac output status of rabbit after pacing with skin colour change on ear and decreased activity, and (c) pacing induced HF rabbit showing oedematous change and lethargic activity. HF = heart failure; LV = left ventricular; T-CMP = tachycardia-induced cardiomyopathy. (Do Young Kim, Sung Hea Kim, Kyu Hyung Ryu. Tachycardia induced Cardiomyopathy, Korean Circ J. 2019 Sep;49(9):808-817. https://doi.org/10.4070/kcj.2019.0199)



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Doxorubicin cardiomyopathy

Doxorubicin has been used to induce many animal species but demonstrates acute and chronic cardiotoxicity. The pathophysiology of doxorubicin-induced heart failure has been attributed to several distinct processes, including the production of free radicals and lipid peroxidation, reactive sulfhydryl groups, binding to channel regulating proteins, and suppression of mRNA and protein synthesis [31]. In this model, rabbits (5–6 kg) of both sexes and different strains can be employed. The sham-creed group receives doxorubicin (1 mg/kg intravenously, twice weekly) for 6 to 9 weeks (untreated group). The test medicine is given to the animals in the test group either subcutaneously or intraperitoneally for 4-6 weeks. The animals are given Pentobarbitone sodium (35 mg/kg intraperitoneally) to make them unconscious once the experiment is over, and their carotid arteries are cannulated to take their blood pressure. While measuring the left ventricular end diastolic pressure (LVEDP) and dP/dt, the heart is exposed, and a cannula is introduced into the left ventricle.

Animals are killed, and the hearts are processed for immunohistochemistry research using Western blot analysis. Prolonged doxorubicin administration to rabbits impairs cardiac contractility and reduces gene expression for the ryanodine receptor (SR), a calcium-induced calcium release channel of the sarcoplasmic reticulum (RYR2). It has been proposed that the heart's production of the C-13 hydroxy metabolite (doxorubicinol) contributes to anthracycline cardiotoxicity. Doxorubicin chronic therapy reduces left ventricular fractional shortening (LVFS) in comparison to age-matched pair-fed controls. In the left ventricle, doxorubicin significantly lowers the ratio of RYR2/Ca-Mg ATPase (SERCA2) mRNA levels. Doxorubicin may be involved in the downregulation of cardiac RYR2 expression in chronic doxorubicin cardiotoxicity, according to this indication. The analysed group is compared to the sham-control group using the characteristics as well as cardiac weight, left and right ventricular weight. The test drug's potential to stop or lessen these alterations is investigated. This paradigm is ideal for examining the functional effects of changed ryanodine receptor expression. Figure 14 Rabbit model of doxorubicin-induced heart failure. (Paulo Vitor Moreira Romãoa , Rhanany Alan Calloi Palozia , Lucas Pires Guarniera , Aniely Oliveira Silvaa , Bethânia Rosa Lorençonea , Samara Requena Nocchib , Cátia Cristina de Freitas Sari Mourac , Emerson Luiz Botelho Lourençoc , Denise Brentan Silvab , Arquimedes Gasparotto Junior. Cardioprotective effects of Plinia cauliflora (Mart.) Kausel in a rabbit model of doxorubicin-induced heart failure. Journal of Ethnopharmacology, Volume 242, 5 October 2019, 112042 https://doi.org/10.1016/j.jep.2019.112042)

Guinea pig model

Aortic banding

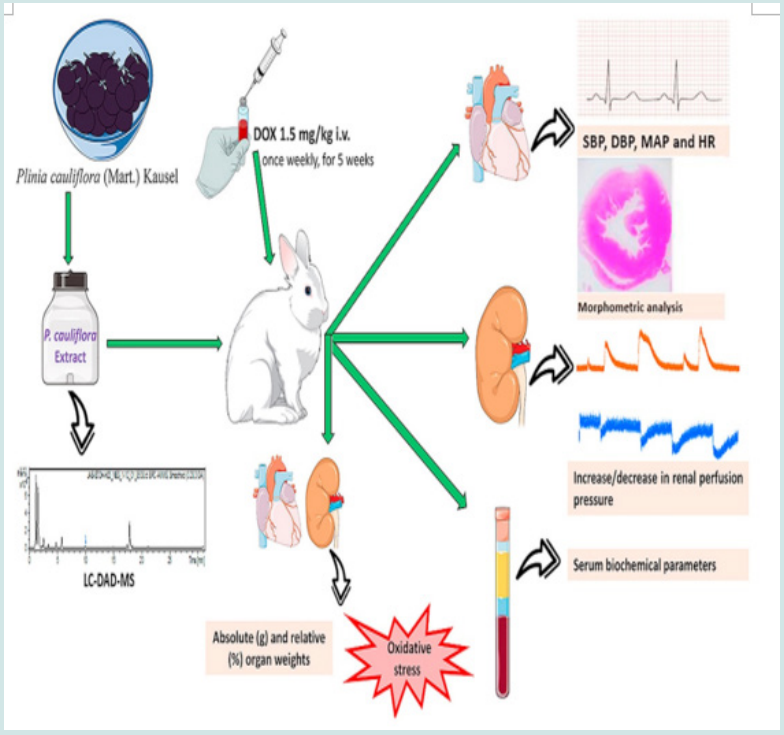

Figure 14: Rabbit model of doxorubicin-induced heart failure
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Cardiac hypertrophy, peripheral oedema, liver, and lung congestion, dyspnoea, hydrothorax, and ascites are the hallmarks of CHF in men. These symptoms have been used to cause CHF in guinea pigs, which exhibits symptoms that are extremely like human pathophysiology. A subset of guinea pigs that have their descending thoracic aortas banded for eight weeks eventually develop overt heart failure. There are some similarities between the altered cardiac function in this guinea pig model and the end-stage failing human myocardium. Using ether, male guinea pigs (weighing 250–400 g) are put to sleep. The pericardium is removed, the chest cavity is opened, and the heart is made visible. The heart is extruded from the thorax while it is still beating, and a ring-shaped clamp with a thin rubber tube is inserted around the base of the heart to keep it from stopping outside of the thorax without closing off the blood circulation. The apical third of both ventricles of the heart are tied off with a thread that has been dipped in diluted disinfectant solution. The loop must be tightened just so, both the loops coming off and complete blood supply cut-off to the apical third resulting in necrosis must be prevented. The incision between the fourth and fifth costal ribs is closed once the clamp is released, and the musculus pectoralis is positioned over the wound. The heart is then repositioned. The skin wound is closed once the thorax is deflated and an antibiotic emulsion has been applied. There are two groups of animals: Group 1 is used as a mock control (untreated group), and group 2 is used as the treated group where (test drugs) are injected into the muscle or subcutaneously supplied for 14 days. Animals in the fictitious control group exhibit CHF symptoms and die at a rate of 80% within a single day. Lung weight and heart weight relative are both much higher. Between 3.5 and 7.5 ml of exudate are discovered in the ascites and thoracic cavity. Histological examination reveals active congestion and pulmonary oedema. Preterminal dyspnoea, tachycardia, and peripheral oedema are seen.

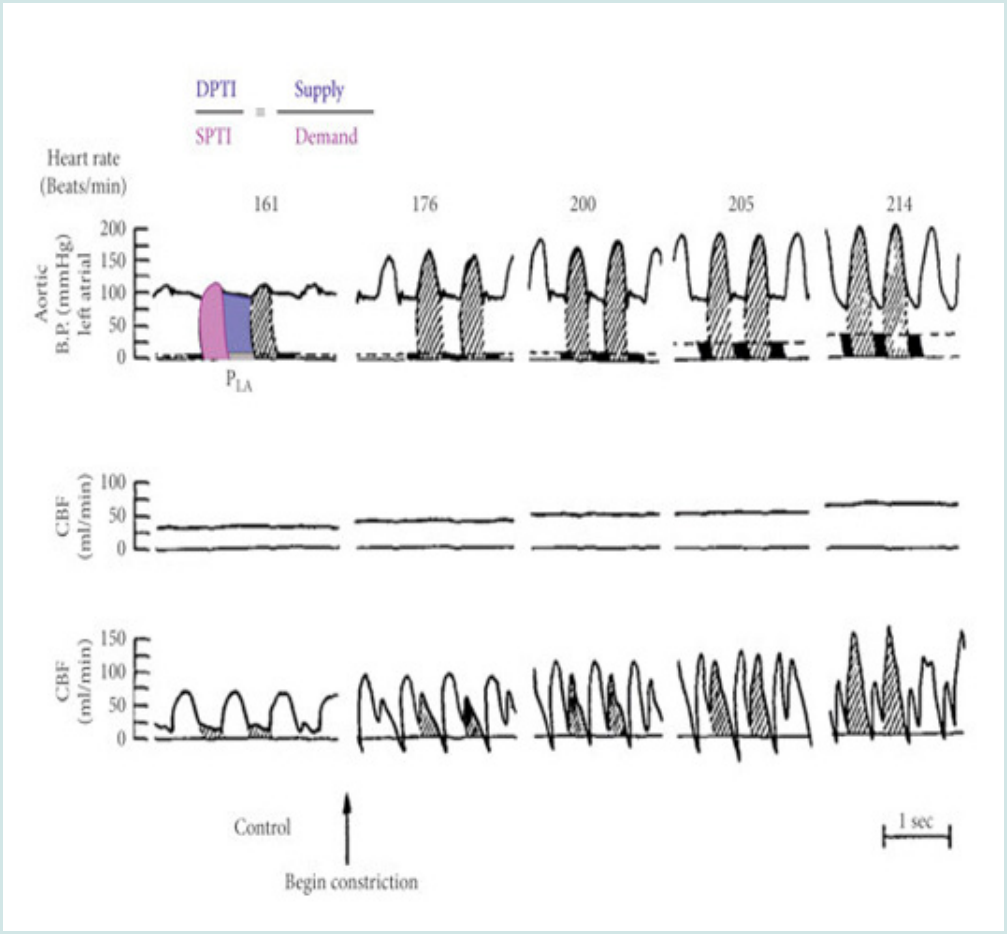


Figure 15: Animal aortic banding model that parallels the development of aortic valvular stenosis: at baseline, the systolic demand (shaded) and diastolic supply (not shaded) are well balanced when recording the aortic and left atrial pressures in this animal model of dynamic, supravalvular stenosis. With progressive banding demand rises (shaded area increases), supply falls (due to acute tachycardia in this animal model but also rising left atrial filling pressures marked as filled areas during diastole). Coronary blood flow (CBF, which corresponds to mean coronary blood flow) begins as diastolic dominant (unique to the normal heart) but concludes as systolic dominant (more typical of a peripheral organ bed.

(Jo M. Zelis, Pim A. L. Tonino, Nico H. J. Pijls, Bernard De Bruyne, Richard L. Kirkeeide, K. Lance Gould, and Nils P. Johnson. Coronary Microcirculation in Aortic Stenosis: Pathophysiology, Invasive Assessment, and Future Directions. Journal of Interventional Cardiology. 2020(9):1-13 DOI:10.1155/2020/4603169)

In addition, after 8 weeks of banding the descending thoracic aorta, lower levels of the proteins SR-Ca ATPase and phospholamban were seen in failing guinea pig hearts compared to an age-matched banded group without clinical indications of heart failure. In terms of myosin isoforms, the guinea pig myocardial, like the human ventricular myocardium, mostly comprises the B-myosin isoform without any of the a-myosin heavy chain seen in hypertrophied and failing hearts. It is researched whether the test substance can undo these modifications [32]. An evaluation of the test drug's survival rate is performed. Regarding calcium cycling, myosin isoforms, and myocardial function, this model is comparable to human heart failure and is suitable for studying the change from cardiac hypertrophy to failure considering changes to the excitation-contraction coupling networks. Figure 15 Animal aortic banding model that parallels the development of aortic valvular stenosis: at baseline, the systolic demand (shaded) and diastolic supply (not shaded) are well balanced when recording the aortic and left atrial pressures in this animal model of dynamic, supravalvular stenosis. With progressive banding demand rises (shaded area increases), supply falls (due to acute tachycardia in this animal model but also rising left atrial filling pressures marked as filled areas during diastole). Coronary blood flow (CBF, which corresponds to mean coronary blood flow) begins as diastolic dominant (unique to the normal heart) but concludes as systolic dominant (more typical of a peripheral organ bed. (Jo M. Zelis, Pim A. L. Tonino, Nico H. J. Pijls, Bernard De Bruyne, Richard L. Kirkeeide, K. Lance Gould, and Nils P. Johnson. Coronary Microcirculation in Aortic Stenosis: Pathophysiology, Invasive Assessment, and Future Directions. Journal of Interventional Cardiology. 2020(9):1-13 DOI:10.1155/2020/4603169)

Syrian hamster model

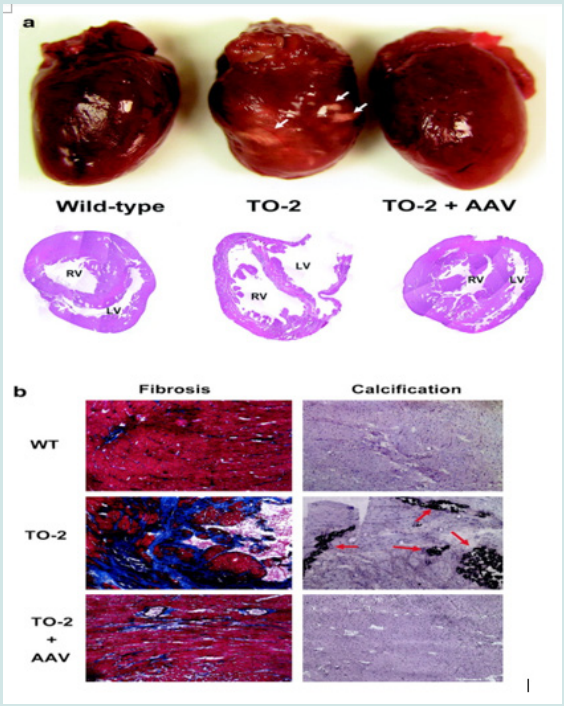
Cardiomyopathic hamster

Syrian hamsters with cardiomyopathic strains are frequently utilised as models for cardiac hypertrophy and heart failure [33]. The model has an autosomal recessive form of inheritance, which causes degenerative lesions in all striated muscles in general and the myocardium. After 7–10 months, the animals exhibit overt heart failure. Histologically, necrotic, calcified cardiac lesions mark the disease's early stages. Moreover, it has been discovered that the expression of myosin isoforms changes throughout time. A prenecrotic stage, in which little pathology is apparent, a phase of fibrosis and calcium deposition, an overlapped time of reactive hypertrophy of the remaining viable myocytes, and a final stage of decreased cardiac function and failure characterise the development of cardiomyopathic illness. This model's benefits include the lack of surgical procedures, minimal cost, and the simplicity with which many animals can be researched. It is significant to note that the time point at which measurements are taken is crucial in this model since there are differences between the strains in the time course of the pathologic alterations. In addition, it appears that the subcellular changes underlying cardiac failure are distinct from those in failing human hearts. Figure 16 Cardiomyopathic Syrian hamster model. (Tong Zhu, Liqiao Zhou, Satsuki Mori, Zhong Wang, Charles F. McTiernan, Chunping Qiao, Chunlian Chen, Dao Wen Wang, Juan Li, and Xiao. Sustained Whole-Body Functional Rescue in Congestive Heart Failure and Muscular Dystrophy Hamsters by Systemic Gene Transfer. Circulation. 2005; 112:2650–2659. Originally published 17 Oct 2005. https://doi.org/10.1161/CIRCULATIONAHA.105.565598)

Transgenic mice model

The pathophysiology of heart failure is now better understood because of recent advances in methods to specifically modify gene expression. Moreover, several genetic models of heart failure in mice that involve the insertion or deletion of genes have been created and miniature physiological procedures have been developed to assess the resulting heart characteristics [34]. These models allow for the evaluation of the molecular pathways behind the genesis and progression of the disease as well as the discovery of genes linked to heart failure. A novel heart failure model is the gene-targeted disruption of the muscle LIM protein (MLP) in mice. The differentiation of the gonads is regulated by MLP. Animals that were homozygous for the MLP deletion experience myocardial hypertrophy and dilated cardiac myopathy. Mature mice exhibit clinical and hemodynamic heart failure symptoms that are comparable to those in people.

Cardiomyopathy development was also noticed in mice lacking gynogenic factor 5 (GF5). Reduced contractility is also shown in transgenic mice overexpressing either B-adrenergic receptor kinase or G-protein coupled receptor kinase 5, which leads to the uncoupling of the B-adrenergic receptor, although without overt clinical indications of CHF. In a recent model of transgenic tropomodulin overexpression, dilated cardiomyopathy with diminished contractile function and heart failure appeared 2-4 weeks after birth. Loss of myofibrillar organization was linked to this [35]. Figure 17 Transgenic mice model. (William F. Elmquist, Donald W. Miller. The Use of Transgenic Mice in Pharmacokinetic and Pharmacodynamic Studies-Minireviews. Journal of Pharmaceutical Sciences, 90(4), 422-435, April 2001 DOI: https://doi.org/10.1002/1520-6017(200104)90:4<422:AID-JPS1001>3.0.CO;2-Z PlumX Metrics)



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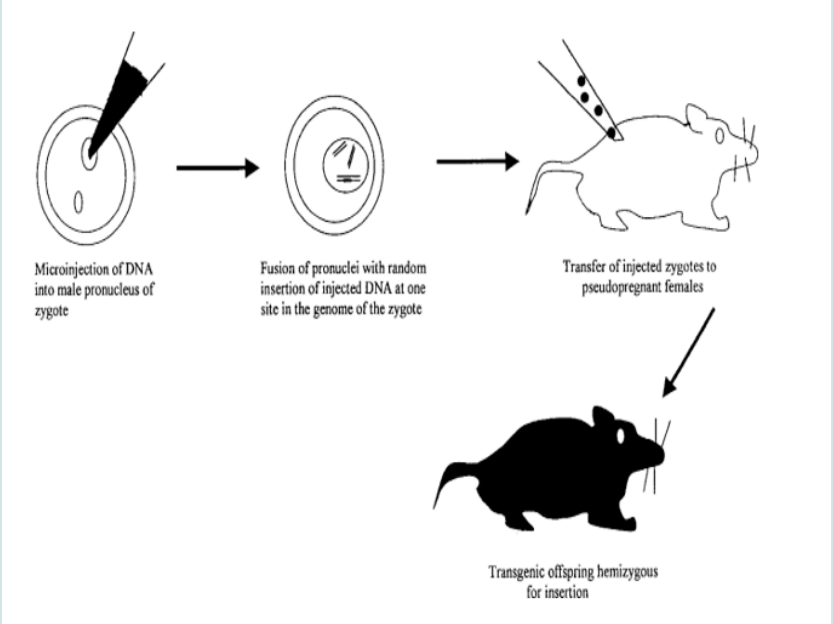

Figure 17: Transgenic mice model

(William F. Elmquist, Donald W. Miller. The Use of Transgenic Mice in Pharmacokinetic and Pharmacodynamic Studies-Minireviews. Journal of Pharmaceutical Sciences, 90(4), 422-435, April 2001 DOI:https://doi.org/10.1002/1520-6017(200104)90:4<422::AID-JPS1001>3.0.CO;2-Z PlumX Metrics).

Conclusion

To assess pathogenesis from the level of the intact-instrumented animal to the tissue homogenate, numerous models have previously been developed in animals with overt clinical heart failure. Many details on hemodynamics, neurohumoral activation, myocardial infarction, and subcellular and molecular changes in the failing heart are revealed by these kinds of studies. Models and species vary greatly, and only a few models accurately represent human heart failure in all of its manifestations. As hemodynamics can now be evaluated in patients, these studies appear to be less essential now than they once were. Moreover, end-stage failing human myocardium became available for functional, biochemical, and molecular biology studies following cardiac transplantation surgery, enabling the assessment of changes prevalent in end-stage failure in human heart itself.

Studying cardiac changes related to compensated, less severe stages of CHF, the change from hypertrophy to failure, or the remodelling process, on the other hand, is relatively challenging or impossible. Animal models are therefore crucial for studying transition events that take place in heart failure. In addition, it may be important to investigate the impact of novel pharmaceutical approaches on homodynamic, neurohumoral activation, and survival using animal models of heart failure. Transgenic animal models of heart failure are currently crucial for understanding the molecular changes underlying the onset of the disease. The discovery of genes that are responsible for heart failure and the evaluation of the ensuing cardiac abnormalities are made possible by the addition or deletion of genes in transgenic mice and to evaluate molecular mechanisms responsible for the development and progression of the disease. Experimental models of CHF hence give most popular animal models, their characteristics, and their significance for new drug discovery for novel Anti- Congestive heart failure agents.

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