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Rodent models of heart failure: an updated review

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Abstract Heart failure (HF) is one of the major health and economic burdens worldwide, and its prevalence is continuously increasing. The study of HF requires reliable animal models to study the chronic changes and pharmacologic interventions in myocardial structure and function and to follow its progression toward HF. Indeed, during the past 40 years, basic and translational scientists have used small animal models to understand the pathophysiology of HF and find more efficient ways of preventing and managing patients suffering from congestive HF (CHF). Each species and each animal model has advantages and disadvantages, and the choice of one model over another should take them into account for a good experimental design. The aim of this review is to describe and highlight the advantages and drawbacks of some commonly used HF rodents models, including both non-genetically and genetically engineered models, with a specific subchapter concerning diastolic HF models.

Keywords Animal models · Rodents · Heart failure · Diabetes mellitus · Cardiovascular research

Introduction

Heart failure (HF) is a complex syndrome in which patients should present the following characteristics: symptoms of HF, signs of fluid retention and objective evidence of an abnormality of the cardiac structure or function at rest [53]. It is often divided in two distinct entities, namely systolic heart failure (SHF) and diastolic heart failure (DHF) or, in alternative, HF with reduced ejection fraction and HF with preserved ejection fraction, respectively. Despite the hot controversy on the definition of each entity, SHF is characterized by an inability of the myocardium to contract and eject blood, while DHF refers to a disturbance in accommodating blood volume during diastole at low filling pressures, due to impaired ventricular relaxation (primarily affecting early diastole) or increased myocardial stiffness (primarily affecting late diastole) [152]. Besides defective myocardial relaxation, the mechanisms underlying DHF include abnormal extracellular matrix dynamics and altered myocyte cytoskeleton, which could interfere with the passive properties of the ventricular wall [152].

The great majority of animal models have been developed for SHF. Besides being rather difficult to replicate pure DHF in animal models, these are also more demanding and time-consuming than SHF. Therefore, not surprisingly most HF models developed so far represent SHF.

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Non-genetically engineered rodent models

Pharmacologically induced cardiomyopathy

Doxorubicin

Doxorubicin (adriamycin, DOX) is an anthracycline widely used in cytostatic treatments. One of the major long-term consequences of DOX therapy is the development of cardiomyopathy and ultimately CHF in humans as in experimental animals. Therefore, understanding the pathogenesis

of cardiotoxic cardiomyopathy is essential to the development of new measures to prevent cardiotoxicity associated with antineoplastic therapies. DOX causes a dose-dependent cardiotoxicity and thus has been used to induce HF in various animal species [21, 37, 291, 293].

DOX administration once a week for 6 weeks or on alternate days for 2 weeks has been shown to induce cardiomyopathy and HF [51, 168, 284]. Interestingly, a single dose of DOX has been shown to induce significant left ventricular (LV) dysfunction in mice after 5 days [189]. This drug is usually administered by intravenous or intracoronary injection. The latter allows delivery of DOX at a smaller dose to induce HF without systemic toxicity [203].

DOX-induced cardiomyopathy is characterized by ventricular wall thinning and dilatation, and depressed systolic and diastolic function [22, 50, 168, 291] accompanied by fluid retention and by neurohumoral activation [8]. At the cardiac muscle level, DOX promotes intrinsic contractile dysfunction and reduced contractile reserve [21, 22, 50]. Furthermore, DOX impairs vascular [208] as well as endocardial [21] endothelial function and [27, 151, 287] induces inflammatory reactions in the heart, leading to thrombosis in the atria and myocarditis [27, 75, 78, 293].

Multiple pathways of anthracycline-induced cardiac cellular injury have been proposed such as the release of cardiotoxic substances, which subsequently accumulate in cardiomyocytes [185], the generation of free radical, lipid peroxidation, and suppression of DNA, RNA and protein synthesis [255, 276]. Other studies suggest that cardiotoxicity pathways include abnormalities in Ca^{2+} handling [50, 54, 285]; induction of mitochondrial DNA lesions [149]; degradation of myofilamental and cytoskeletal proteins, including titin [160] and dystrophin [40]; interference with various pro-survival kinases [224]; and changes in adrenergic and adenylate cyclase function [33, 74]. These examples of a much larger set of proposed cardiotoxic mechanisms are not mutually exclusive: they may each contribute to cardiac cell damage, ultimately leading to myocyte death, by either necrosis or apoptosis [254]. Additionally, it was recently demonstrated that DOX cardiomyopathy can be also mediated by depletion of the cardiac stem cell pool and rescued by restoration of progenitor cell function [50].

Spontaneous hypertensive rats (SHR) are more sensitive to the toxic effects of DOX [98], probably because of the low free radical–scavenging ability of their myocardium [122].

DOX model has a short time course of induction of HF and also the advantages of being technically simple, reproducible, non-invasive and economical. Additionally, it can be used in several animal species to promote either chronic or acute HF [203]. The main limitations of this model are related to the variable degree of ventricular dysfunction and the high incidence of arrhythmias that contribute to the high mortality rate. Anthracycline administration also has undesirable bone marrow, gastrointestinal and renal toxicities that can however be eliminated by the intracoronary injection of the drug [8, 203].

Homocysteine

Hyperhomocysteinemia has been identified as a causative factor of cardiac stress and dysfunction in both spontaneous hypertensive and normotensive rats [129, 130]. In rats, supplementation of diet with homocysteine for 10 weeks produces hyperhomocysteinemia and consequently ventricular dysfunction with compromised systolic and diastolic function [52, 130]. The main factors involved in the development of HF are oxidative stress and inflammatory mediators [129].

Isoproterenol

Excessive doses of catecholamines produce diffuse myocardial destruction with cardiomyocyte necrosis and extensive fibrosis in both animals and humans [219, 220, 292]. The mechanism underlying myocardial damage is likely related to an imbalance between oxygen supply versus demand due to myocardial hyperactivity [62]. In mice, infusion of isoproterenol for 7 days has been shown to induce cardiac dysfunction [216]. In rats, subcutaneous administration of isoproterenol for 3 days leads to a dose-dependent impairment of cardiac function and neurohumoral activation [88, 325], with cardiomyocyte necrosis and extensive LV hypertrophy and dilation and after 2 and 12 weeks, respectively [92, 324]. However, isoproterenol administration before ischemia exerts a cardioprotective effect in rats [92]. The advantages of this model are its technical simplicity and excellent reproducibility in association with a satisfactory low mortality. Nonetheless, it seems not suitable for inducing an overt state of CHF because higher doses of catecholamines can increase the mortality rate up to 80% [88].

Monocrotaline

Monocrotaline (MCT) is a plant toxin derived from *Crotalaria spectabilis* that can be administered by intraperitoneal, subcutaneous or intravenous injection to induce right ventricular dysfunction and HF within 4–6 weeks [30, 299]. Current hypotheses of the pathogenesis of MCT-induced pneumotoxicity suggest that MCT is transformed in a bioactive pyrrole metabolite in the liver and is then transported by red blood cells to the lung, where it initiates endothelial injury. The metabolite has a half-life of $\sim$3 s in aqueous media and primarily affects the pulmonary

vascular bed as lungs are the first major vascular bed after the liver [230]. Nonetheless, MCT can injury other structures such as liver [135] or kidney [262]. In the pulmonary vasculature, MCT induces perivascular inflammation, platelet activation and endothelial dysfunction, generally leading to increased pulmonary arterial pressure. These changes are accompanied by increase in RV systolic and diastolic pressures, hypertrophy and ultimately HF [99, 310]. Besides inducing HF, MCT is a simple model which, at an earlier phase, shares some similarities with human pulmonary hypertension.

Myocardial infarction-induced HF

Since ischemic heart disease is the most important cause of human HF, coronary artery occlusion is the most common method of inducing acute myocardial damage in animal models. Ligation of the left anterior descending (LAD) coronary artery or one of its branches remains the most preferred and acceptable method of inducing regional injury and subsequent HF in rodents [10, 85], as well as to gain further insight into pathophysiology of post-myocardial infarction (MI) cardiac remodeling [12, 223]. The mechanisms responsible for cardiac remodeling are mostly related to changes in extracellular matrix of the remaining overloaded myocardium and neurohumoral activation [72, 156, 234].

Surviving mice gradually develop HF within the 4 weeks following the surgical procedure [76, 155, 158]. In rats, a significant decrease up to 25% in cardiac output is observed 8 weeks after LAD ligation [115]. The infarct size varies significantly (between 10 and 45%) and is directly related to the degree of LV function impairment [228], influencing the time course of CHF development [10]. Generally, the infarct extension needs to affect at least 30% of the LV mass in order to present the typical characteristics of CHF and to induce considerable increases in the molecular markers of hypertrophy [10]. Age also exerts a noteworthy effect on the time course of CHF development, with young animals tolerating well LAD ligation without CHF signs, in spite of the larger infarct size [85]. Some recent studies showed that female mice undergo less extensive ventricular remodeling, suggesting the influence of sex hormones as a putative explanation for gender differences [315].

In both mice and rats, mortality ranges between 35 and 50% and occurs within the first hour after MI due to ventricular fibrillation and severe acute HF [79, 144]. Furthermore, in rats, it seems to be strain dependent with Lewis inbred rats surviving more than Sprague–Dawley rats [164].

Contrary to the clinical situation, in which the patient has progressive non-occlusive coronary artery obstruction, myocardial infarct in this model is due to the sudden occlusion of a normal coronary artery. Therefore, efforts have been made to create a model of chronic myocardial ischemia, more similar to the clinical reality. Indeed, a mice model of hyperlipidemia and atherosclerosis with multiple infarction and CHF has been described. However, those high-density lipoprotein receptor SR-B1 and apolipoprotein-E double knockout mice survive only few weeks after birth limiting their use in HF research [23].

Protocols of temporary LAD occlusion have been developed to reproduce human ischemia–reperfusion injury. This model has confirmed the benefits of reperfusion since infarct size was found to be significantly lower than after permanent occlusion of the coronary artery. However, they also revealed the diversity of results as a consequence of mouse left coronary anatomic high variability [187].

The procedure was further modified to analyze ischemic preconditioning of the heart. In this method, LAD is repeatedly occluded to subject the heart to several rounds of brief ischemia and reperfusion before permanent occlusion. Molecular analyses identified various ischemia-induced genes that confer tolerance to subsequent ischemic event [311].

The cost and simplicity confer important advantages to LAD ligation. On the other hand, rat differs from human in terms of electrophysiology, coronary circulation, cardiac protein isoforms and time course of MI evolution. In fact, available data point to a faster onset of healing and termination processes in rats [142], which mean results must be interpreted with caution.

An alternative model of MI was cryoinfarction, which induces a series of cryoinjuries in the epicardium of mice and rats [245]. However, it has not caught the interest of the scientific community, and thus, it is no longer used.

Myocarditis-induced HF

Viral myocarditis is a common cause of dilated cardiomyopathy and HF. The coxsackie-B3 virus (CB3) and the encephalomyocarditis virus (EMCV) have been used to induce myocarditis in rodents [102, 213, 318]. EMCV infection can lead to myocyte necrosis and significant biventricular dilation during the phase of viremia, while typical signs of CHF appear after 7–14 days of virus inoculation [68, 177, 213]. This model is limited to Balb/c and DBA/2 mice because other mouse strains are resistant to virus infection [306]. Virus inoculation in genetic engineered mice has been shedding light on the molecules involved in the pathogenesis of viral myocarditis. Indeed, the administration of an exogenous antitumor necrosis factor-α (anti-TNF-α) antibody reduced myocardial lesion and improved survival, mitigating the effect of the

observed increase in TNF-α expression [178]. A retrovirus model of encephalitis and myocarditis in mice showed that nuclear factor-kB activation confers protection against virally mediated apoptosis and its expression is preserved in the presence of interferon-β. The absence of any of these molecules in the myocardium leads to striking viral infection and cell death [214]. Transgenic knockout models of components of the immune system have provided interesting insights in the pathogenesis of viral myocarditis [163].

Another pathogenic agent capable of causing myocarditis and dilated cardiomyopathy is the protozoan parasite *Trypanosoma cruzi*, which causes Chagas disease, a major form of HF in Latin America [46]. The infection causes generalized vascular inflammation, which stimulates the production of endothelin-1 and thromboxane-A2, further enhancing coronary vasospasm and myocardial ischemia [35].

Autoimmune myocarditis has been induced by an immunization process with different intracellular antigens. In rats, hemodynamic deterioration and myocarditis have been reported after 3 weeks of immunization with cardiac α-myosin or α-myosin peptides [173, 305]. This was associated with increased expression and activity of inducible nitric oxide synthase (iNOS) and an inhibitor of that enzyme effectively attenuated the histopathologic changes, thus pointing to a relevant pathophysiologic role of nitric oxide (NO) [103, 104]. In mice, immunization with a monoclonal anti-dog SERCA2a antibody caused myocarditis [93].

Immunization of mice with recombinant murine cardiac troponin I (mcTnI) resulted in myocardial deposition and elevated serum levels of anti-mcTnI autoantibodies, accompanied by myocardial inflammation (both humoral and cellular immune response), cardiac dilatation, contractile failure and increased mortality rate [83].

Systemic hypertension-induced HF

Spontaneously hypertensive rats (SHR)

Systemic hypertension is another relevant factor in human CHF. Spontaneous hypertension is a natural model of pressure overload, in which systemic hypertension leads to HF with aging. Hypertensive vascular lesions appear within 6–7 weeks, being more severe in males than in females. For the first 12 months, the hypertrophy is compensated and contractility is preserved, but after 18–24 months, there is overt CHF characterized by fibrosis, LV dilation and reduced systolic function [13, 100, 226]. These structural and functional changes occur in tandem with a marked raise in cytokine levels such as TNF-α and interleukin-6 [223]. Transition to failure has been suggested to depend on significant alterations in the expression of genes encoding extracellular matrix proteins, oxidative stress and increased apoptosis of myocytes [1, 13, 15, 157, 273]. The gradual onset of hypertension with aging makes this model suitable for studying the transition from hypertrophy to CHF and for reproducing hypertension-induced CHF in humans [194]. It has the advantage of avoiding the complications associated with surgical or pharmacologic interventions, while mimicking the changes found in human essential hypertension [16, 19]. Nonetheless, the long period required for developing CHF poses a great limitation, making it a time-consuming and consequently an expensive model. Additionally, this model has other two relevant drawbacks, namely the absence of an appropriate control and the complexity of the genetic mutations, which have affected not only blood pressure but many other regulatory systems as well.

The SHR stroke prone (SHR-SP) is a further developed substrain with even higher levels of blood pressure and a strong tendency to die from stroke [319].

Spontaneously hypertensive HF-prone rats (SHHF)

Spontaneous hypertensive rats carry the *facp* corpulent gene, which encodes a defective leptin gene, and therefore, they develop obesity and HF [41, 188]. The time for the development of HF depends on *facp* gene dosage and gender (male animals are more prone to HF than females [96]) but, in general, SHHF rats present HF earlier than the SHR strain, with loss of cardiac function starting at the age of 15 months [100]. These animals present alterations in the renin-angiotensin-aldosterone system (RAAS) and also in calcium metabolism [82, 107, 188, 222]. The greatest advantage of this strain is the possibility of studying drug interventions in an extended range of cardiovascular risk factors like obesity, diabetes and renal dysfunction [259].

Dahl-salt-sensitive rats

This is a mutant strain of Sprague–Dawley rats that are characterized by hypersensitivity to sodium intake [48]. When placed on a high-salt diet from the 6th week of age, they develop concentric LV hypertrophy without chamber dilation around the 11th week and decompensate HF with marked ventricular dilation between the 15th and the 20th week [119, 139]. Failure is associated with reduced myocardial performance as evidenced by the lower performance of muscle strip preparations and the short lifetime of failing rats [119]. Diastolic dysfunction, as well as increased LV endothelin-1 production, collagen accumulation and even survival could be improved more effectively by a combination of angiotensin receptor blockers

and angiotensin-converting-enzyme (ACE) inhibitors than either agent alone [137].

Interestingly, it has been shown that introducing high-salt diet at 7 or 8 weeks of age can result in distinct HF phenotypes. Indeed, the 7-week starting rats showed a steep elevation in blood pressure and progressive LV hypertrophy, falling into overt DHF at approximately 19 weeks. On the other hand, the 8-week starting rats showed a gradual rise in blood pressure and less progressive LV hypertrophy, developing SHF at approximately 26 weeks. Therefore, these two different models of overt HF may be useful as models of isolated DHF and SHF based on the same hypertensive heart disease, which could be relevant to the pathophysiologic and molecular characterization of each HF subtype [55]. Another report found that the development of HF was dissociated from changes in passive diastolic and active systolic properties, suggesting that volume overload plays an important pathophysiologic role in the development of HF despite preserved overall ventricular pump function in this model of chronic hypertension [139].

This model is suitable to study the transition from compensated hypertrophy to failure. Moreover, it is often used to identify the role of several pathways and molecular mechanisms like oxidative stress, extracellular matrix degradation [289], calcium handling impairment [253] as well as redox-regulated transcription factors [116] and apoptotic factors activation [320].

DOCA-salt rats

The deoxycorticosterone acetate (DOCA) salt-induced model of hypertension is a typical representative of pharmacologically induced hypertension. A very high subcutaneous dose of DOCA is required to induce hypertension in rats [268]. Isotonic saline is the sole drinking fluid, which hastens and aggravates progression to hypertension [280]. Despite being salt-dependent in its initiation, this model frequently needs surgical reduction of renal mass or unilateral nephrectomy. DOCA-salt hypertension is a low renin and volume-overloaded form of hypertension. The combination of DOCA-salt and unilateral nephrectomy results in hypertension, renal hypertrophy, nephrosclerosis, cardiac hypertrophy and myocardial and perivascular fibrosis within 4–5 weeks of chronic treatment [89, 215].

The pathophysiologic mechanisms underlying the development and maintenance of DOCA-salt hypertension include increased levels of arginine vasopressin [120], angiotensin-II/aldosterone [300, 313], endothelin [179, 204, 258, 302] and oxidative stress [154, 175], excessive activation of the sympathetic nervous system [132] and nitric oxide synthase (NOS) uncoupling due to oxidative depletion of its cofactor tetrahydrobiopterin (BH4) [274]. Indeed, both inhibition of the angiotensin-aldosterone system and endothelin receptor blockade have been shown to prevent cardiac remodeling, even without concomitantly reducing arterial blood pressure [89, 257]. Of notice, PPAR-α activation has also a beneficial effect on myocardial fibrosis and prevented diastolic dysfunction in DOCA-salt rats by modulation of NF-κB inflammatory pathway [215]. Nonetheless, the cardiac consequences are minimal during the development of DOCA-salt hypertension-induced hypertrophy [29]. This is in contrast to the decreased responses reported in other rat models of cardiac hypertrophy and in the failing human heart. Therefore, hypertrophy in hearts of DOCA-salt hypertensive rats does not produce similar changes to the failing human heart [29].

Of notice, a group recently published a mouse model that combines a surgical intervention to induce pressure overload, namely transverse aortic constriction (TAC), with DOCA administration, in the setting of normal-salt diet. Compared with TAC mice, TAC plus DOCA mice had similarly normal LV systolic pressure and fractional shortening but more hypertrophy, fibrosis and diastolic dysfunction with increased lung weights, consistent with HF with preserved ejection fraction. There was progressive activation of markers of oxidative stress but no evidence of classic mineralocorticoid receptor–dependent gene transcription. Therefore, they suggest that pressure-overload hypertrophy sensitizes the heart to mineralocorticoid excess, promoting the transition to DHF without activation of the classic mineralocorticoid receptor-dependent gene transcription.

The major limitations of the DOCA-salt model are (1) the need to employ a large amount of drug, (2) the requirement for surgical reduction of renal mass and (3) the dependence on a strictly controlled ingestion of a high NaCl dose. On the other hand, its chief advantage is the potential to investigate the role of sodium in the developmental stages of hypertension.

2K1C rat

Since 1934, when Goldblatt and his co-workers induced an elevation of blood pressure by partial constriction of the renal artery of the dog [81], many successful models of renal-induced experimental hypertension have been developed in rats. In general, the procedure includes two-kidney Goldblatt hypertension (constriction of one renal artery while the contralateral kidney is left intact) and one-kidney Goldblatt hypertension (one renal artery is constricted and the contralateral kidney is removed) [280]. Clipping one renal artery, while leaving the contralateral kidney untouched, induces systemic hypertension and LV concentric remodeling within 8 weeks [131]. Histologic studies revealed extensive LV fibrosis, while echocardiography and hemodynamic data consistently shown diastolic dysfunction [131]. Indeed, inhibition of matrix

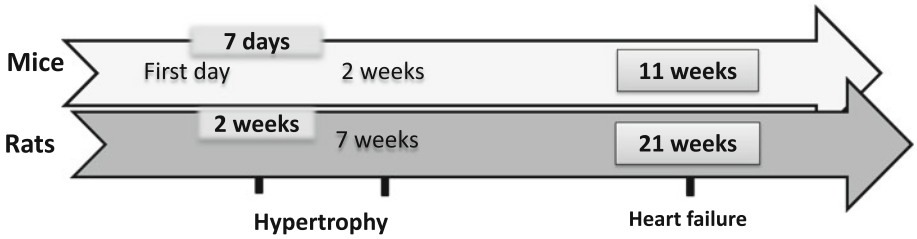

Fig. 1 Timeline progression of transverse aortic constriction: comparison between mice and rat

metalloproteinase activity in these hypertrophic hearts has been shown to provide beneficial effects in terms of structure and function [237]. At cellular level, several changes in the energy metabolism, actin–myosin cross-bridge cycle and protein expression were identified in renovascular hypertensive rats [131]. In addition, the paramount role of activation of the RAAS [73, 150] and the sympathetic nervous system [32, 270] has been thoroughly studied. In the one-kidney model, no compensatory increase in sodium and water excretion can occur, and hence, fluid volume is retained, which means this model is thus a sodium-fluid volume-dependent model. Therefore, it would advantageous for studying the role of volume expansion in the development of hypertension [11]. During the early developmental stage, when the clip is removed, arterial blood pressure returns to normal in both models, suggesting that renovascular hypertension is both reversible and reproducible [147].

Pressure-overload-induced HF

Aortic constriction (banding) is a well-established surgical technique for induction of LV chronic pressure overload and hypertrophy in rodents. The banding initially imposes little or no restriction to aortic flow but gradually, as the animal grows, the relative severity of the constriction increases, resulting in cardiac hypertrophy. Aortic banding in several positions has been used to mechanically reproduce the cardiac consequences of aortic stenosis, systemic hypertension and coarctation of the aorta [111, 138, 203, 240, 279]. The constriction can be thoracic, either close to the origin of the aorta, ascending aortic constriction (AAC), or in the aortic arch between the first and second trunks and named transverse aortic constriction (TAC). Alternatively, the constriction can be performed in abdominal aorta, either below or above the renal arteries, the latter inducing hypertension by renal hypoperfusion and concomitantly LV hypertrophy [34]. The anatomic location of the constriction is the main responsible for the differences between these models. In this context, AAC is generally used to study the effects of early insult due to pressure overload, while TAC and suprarenal aortic constriction display a more gradual rise of pressure, progression toward hypertrophy and HF [16].

The timeline of disease progression depends on the selected species, age or gender, with mice subjected to TAC presenting LV hypertrophy as early as 7 days [294] and decompensate HF at 4 weeks [153], while rats present slower progression [16], as illustrated in Fig. 1. For instance, in weanling rats [70, 263, 309, 316], a TAC surgery that reduces 50% of the aorta diameter creates a systolic pressure gradient of $\sim$50–60 mmHg between the aorta and the LV, inducing clear echocardiographic evidence of LV hypertrophy, and increases left atrial pressure around the 8th week [162]. After 18–20 weeks of compensated LV hypertrophy, a subgroup of animals eventually decreases LV systolic pressure, accompanied by increased LV volume, reduced ejection fraction and clinical signs of overt CHF [309]. Moreover, molecular changes have been reported with increased expression of β-myosin heavy chain, atrial natriuretic peptide (ANP), interleukin-1, interleukin-6 and TNF-α [200]. On the other hand, the failing myocardium exhibits a reduced expression of SERCA2a when compared to non-failing hypertrophied heart, which suggested that decreased levels of SERCA2a could be a marker of transition from compensatory hypertrophy to failure in these animals [70].

Abdominal aortic banding in rats causes an initial increase in contractility due to the compensatory activation of the sympathetic nervous system [25] but after 8 weeks, systolic and diastolic dysfunction as well as concentric hypertrophy are evident [34, 67]. In mice, suprarenal abdominal aortic banding causes cardiac hypertrophy within 4 weeks as a compensatory response, which eventually leads to CHF after 15–21 weeks depending on the degree of constriction as well as animal age, gender and weight [94, 312]. Changes in NO pathway are believed to play an important role in the pressure-overloaded heart and pathologic cardiac remodeling. In fact, reports showed that phosphodiesterase-5 (PDE5) inhibitor sildenafil reduces LV hypertrophy and dilation in the mouse TAC model [223, 290]. However, the most promising therapeutic approach is represented by a new neutral sugar organic nitrate, LA-419, the thiol group of which seems to protect NO from degradation, thereby increasing its bioavailability. In the aortic stenosis model, LA-419 has been found to restore the complete NO signaling cascade and reduce LV remodeling, but without restoring the original pressure

gradient, indicating a possible direct antiproliferative effect [243]. Additionally, the exogenous administration of the NOS cofactor BH4 has been shown to reduce LV hypertrophy, fibrosis and cardiac dysfunction in mice with pre-established pressure overload. In this setting, BH4 recoupled endothelial NOS, with subsequent reduction of NOS-dependent oxidative stress and reversal of maladaptive remodeling [195, 196].

Among the major advantages that these banding models share compared to other hypertensive or HF models is the ability to manipulate the degree of pressure overload by changing the constriction severity [197]. Concerning the thoracic aorta constrictions, the main advantage is the similarities to human HF progression, especially to aortic stenosis patients. Accordingly, it is characterized by initial compensatory phase, with concentric LV hypertrophy followed by an enlargement of cardiac chambers associated with a further deterioration of LV function [16]. Another advantage is the extensive information regarding TAC model: it was first described in 1994 by Rockman [240], and it has been extensively used since then, especially in mice either by traditional thoracotomy approach [67, 239] or by minimally invasive aortic banding through a small incision in the proximal sternum [111]. Finally, this method permits the quantification of the pressure gradient across the aortic constriction and the stratification of LV hypertrophy [223]. However, the rat TAC model has several drawbacks such as prolong duration of the protocols (Fig. 1), inter-individual variability in the response to pressure overload [198] and high proportion of debanding due to internalization of the constriction knot [171]. These two last disadvantages require the use of large experimental groups and the use of accessory methods for visualization of the constriction integrity and progression of disease, such as echocardiography. Both AAC and TAC models have a common disadvantage resultant from the complex surgical method and equipment necessary for open-chest microsurgery. The lack of such an extended learning curve is the major advantage of abdominal constriction model, alongside with the low mortality rate associated with banding (10%) [70]. Activation of RAAS might however limit the use of abdominal aorta constriction in some studies [241]. Moreover, decrease of LV relaxation rates makes such models valuable for the evaluation of diastolic dysfunction, which is an important factor in the progression of LV failure [69]. In addition, the stimulus for HF is gradual in onset as is the progression from compensated hypertrophy to HF in humans, thus making it clinically more relevant. Recently, a minimally invasive murine model of TAC debanding was described, in which it is possible to remove the band up to 4 weeks later through the same suprasternal incision [278]. This reversible model of pressure overload turned out to be an interesting model to study the molecular mechanisms involved in LV reverse remodeling.

Volume-overload-induced HF

Arteriovenous shunts have been used to induce volume overload and consequently dilated cardiomyopathy and HF in rodents. Femoral artery to femoral vein fistulas lead to HF, but present a reported mortality above 25% in all studies [217]. The more recent aortocaval shunt is a relatively simpler and faster alternative to induce HF with good survival rates and no need to perform thoracotomy [28, 77, 231]. In rats, significant cardiac hypertrophy develops 4 weeks after shunt induction, with compromised LV contractility and increased end-diastolic pressure [256]. Severe volume overload from a large aortocaval fistula initially leads to depressed LV function followed by a compensatory hypertrophy and near normal function at 4 weeks [165, 307]. Decompensated hypertrophy or CHF develops between 8 and 16 weeks after the intervention and is characterized by a decline in systolic and diastolic function [34, 308] and a shift between myosin heavy chain isoforms expression [307]. Nonetheless, shunt closure has been reported in 7% of the cases, which means that it is necessary to confirm the patency of the shunt at the end of investigation. Of note that, not only the duration, but also the size of the shunt will determine the onset and severity of CHF in rats, with elevation of LV end-diastolic pressure reported only in the overt CHF group caused by a large shunt for a minimum period of 4 weeks [148]. This procedure has the advantage of being fast and usually well tolerated, despite the limitation of requiring a laparotomy.

Another procedure used to induce volume overload in rats is aortic valve regurgitation, in which an aortic valve cusp is punctured [56, 207].

The neurohumoral activation of volume-overload models includes local activation of RAAS, which is associated with depressed myocardial function [211]. Recent reports found that ANP expression is a more sensitive marker of volume overload than pressure overload [36]. In addition, long-term overexpression of SERCA2a in this animal model can preserve systolic function and potentially prevent diastolic dysfunction and LV remodeling [134].

Diabetic cardiomyopathy-induced HF

Animal models have been extensively used in diabetes research. Their utility can be questioned due to species differences; however, rodent models share many features with human diabetic cardiomyopathy. For example, rodent models of obesity, insulin resistance and type 2 diabetes present LV hypertrophy, diastolic dysfunction, increased cardiac fatty acid uptake and utilization, decreased cardiac

efficiency, impaired mitochondrial energetics, increased myocardial lipid storage, and impaired Ca^{2+} handling [4, 19, 31].

There are a number of pharmacologic rodent models of diabetes: streptozotocin (STZ) administration to rats or mice, which induces diabetes mellitus (DM) as soon as 48 h post-injection [295]. This substance is selectively toxic to β-cells in the pancreatic islets, induces insulin deficiency and hyperglycemia and therefore represents a model of type 1 diabetes.

On the other hand, selective inbreeding has produced several strains of animal that are considered reasonable models of type 1 diabetes, type 2 diabetes and related phenotypes such as obesity and insulin resistance (Table 1). Apart from their use in studying the pathogenesis of the disease and its complications, all new treatments for diabetes, including islet cell transplantation and preventive strategies, are initially investigated in animals. In recent years, a large number of new genetic animal models for the study of diabetes, including knock-in, generalized and tissue-specific knockout mice, have been described. Rodent models of type 2 diabetes include the Zucker fatty rat, as well as db/db and ob/ob mice, all of which display dysfunctional or absent leptin homeostasis and therefore develop insulin resistance in different timepoints.

In vivo studies in these rodents have revealed susceptibility to systolic and diastolic dysfunction using echocardiography and hemodynamic measurements [301]. They also exhibit a propensity to ischemia/reperfusion injury following LAD ligation, which occurs in conjunction with structural and functional changes to the LV [87]. However, there are several limitations when comparing these models to human diabetic cardiomyopathy, as spontaneous ischemia and atherosclerotic disease are not prominent in rodents [18]. The latter becomes simultaneously a valuable aspect as the effects of obesity, insulin resistance and diabetes on the heart can be studied independently of coronary artery disease [121]. Importantly, rodent models present fulminant and uncontrolled hyperglycemia or insulin resistance, while in the clinical setting patients with diabetes are increasingly well controlled as demonstrated by a recent study which found no evidence for diabetic cardiomyopathy in well-controlled patients with type 1 diabetes [141]. Moreover, because DM develops at varying stages in these models, it is important to keep in mind that studies performed in animals before the onset of diabetes may reflect changes that are secondary to the underlying obesity and insulin resistance, and studies performed after the onset of diabetes may reflect the added effects of hyperglycemia of different durations.

In conclusion, each model has certain limitations and no perfect model exists that exactly mimics human diabetic cardiomyopathy (Table 1).

Diastolic HF models

In spite of the rising prevalence of DHF, currently there is no evidence-based treatment strategies capable of changing its natural history, reflecting our poor understanding of this HF subtype [314]. Therefore, animal models of diastolic dysfunction and DHF urge for the development and preclinical evaluation of new effective therapies for this disease. However, animal models of DHF are rather scarce, thus leading to the utilization of diastolic dysfunction models, which are more widely published and very similar regarding the basic pathophysiologic mechanisms [60]. Furthermore, these models have been most commonly created in large animals, such as canine, sheep and swine. Nonetheless, there have been some successful rodent models that deserve to be highlighted in this review.

Animal models have tried to reproduce the paramount risk factors typically associated with diastolic dysfunction and DHF, namely aging, diabetes mellitus and hypertension [327]. In fact, the alterations in myocardial relaxation and stiffness associated with chronic hypertension and diabetes have been already mentioned above in the appropriate models, namely Dahl-salt-sensitive rats, DOCA-salt rats and diabetic cardiomyopathy.

Despite the great difficulty in developing an animal model of DHF age-induced, a recent study has characterized a model demonstrating isolated diastolic dysfunction associated with accelerated aging [235]. This mouse model is a spontaneous senescence model that displays many common geriatric disorders in the human population and recapitulates diastolic dysfunction as it naturally occurs in the elderly. Diastolic dysfunction, accompanied by fibrosis and an increase in pro-fibrotic cytokines, develops between 3 and 6 months of age, which is an early timepoint in the life span of these animals. This suggests that the physiologic abnormality manifests over a relatively short period of time and, from an experimental standpoint, adds an advantage as it allows for a more rapid study of pathophysiologic mechanisms. The senescence-accelerated mouse model will probably turn to be a useful model for future studies of age-related diastolic dysfunction, since the better insight into its underlying mechanisms could pave the way for designing specific pharmacologic strategies to prevent or treat this pathology [235].

The association between aging and diastolic dysfunction had already been addressed in a previous study, which compared adult (6-month-old) and old (24-month-old) Fischer 344/BNF1 rats after either 12 weeks of treadmill training or normal sedentary cage life [26]. Echocardiographic indices of LV relaxation were significantly lower in the old rats, but with training, they increased back to the levels seen in the adults. LV stiffness measured in isolated perfused hearts was not affected by age or training, but

Table 1 Summary of the characteristics of the most usual diabetes mellitus animal models

Model	Type	DM type	Species	Pathophysiologic changes	Advantages	Disadvantages	Ref.
Alloxan	P	1	Mouse Rat	Significant hyperglycemia Ketosis and/or ketoacidosis Glycosuria, hyperlipidemia, polyphagia, polydipsia Neuropathy and cardiomyopathy	Fast, economic and consistent	High mortality rate Alloxan has a very short half-life (<1 min) Hyperglycemia frequently reverts by pancreatic regeneration	[236]
Streptozotocin	P	1	Mouse Rat	Significant hyperglycemia Polyuria, polydipsia Muscular atrophy Neuropathy	Fast, economic and consistent	High mortality rate Very severe model	[232]
OLETF—Otsuka Long-Evans Tokushima Fatty	G	2	Rat	Hyperglycemia Polyuria, polydipsia Mild obesity Diastolic dysfunction Diabetic nephropathy with nodular glomerulosclerosis (30 wk)	Progressive DM: Initial phase (0–9 wk): Pancreatic islet hyperplasia and lymphocytes' infiltration Intermediate phase (10–40 wk): Pancreatic islet fibrosis Advanced phase (>40 wk): pancreatic islet atrophy. Type 1 DM	Late DM development Only males develop DM	[133]
ZDF—Zucker Diabetic Fatty	G	2	Rat	Dysfunctional leptin receptor Hyperphagia, hyperlipidemia, hyperglycemia Glucose intolerance and hyperinsulinemia (10−12 wk) Mild hypertension and obesity Decreased GLUT4 expression (25–55%) Impaired cardiac contractility and diastolic function (∼ 20 wk) Increased LV mass and fatty acid oxidation	Very common model ZDF were selectively bred from Zucker fatty rat, which are similar but without hyperglycemia	Hydronephrosis Due to different genetic backgrounds, no comparisons can be made between ZDF and Zucker fatty rats	[125]

Table 1 continued

Model	Type	DM type	Species	Pathophysiologic changes	Advantages	Disadvantages	Ref.
GK—Goto-Kakizaki	G	2	Rat	Mild fast hyperglycemia Hyperinsulinemia and insulin resistance Decreased insulin production Retinopathy, microangiopathy, neuropathy and nephropathy	Stable degree of glucose intolerance Useful for studying advanced diabetic nephropathy Wistar rats are the control group	Non-obese	[84]
Wistar Fatty	G	1/2	Rat	Hyperglycemia, hyperlipidemia, hyperinsulinemia (12 wk) Glucose intolerance and insulin resistance Hypertension (16 wk) Wistar × Zucker selective breeding	Wistar rats are the control group	Only males develop type 2 DM Not commercially available	[136]
Db/db	G	2	Mouse	Leptin receptor deficiency Hyperlipidemia and obesity (8 wk) Polyphagia, polyuria and polydipsia Hyperglycemia (8 wk) and hyperinsulinemia (2 wk) Peripheral neuropathy Diabetic cardiomyopathy Impaired diastolic function, mitochondrial energetic, Ca^{2+} homeostasis and cardiac efficiency Increased LV mass, fatty acid oxidation and RAAS activation	Advantages associated with mice reduced size (see text)	Glucose levels progressively increase until the 16th week	[38]

Table 1 continued

Model	Type	DM type	Species	Pathophysiologic changes	Advantages	Disadvantages	Ref.
Ob/ob	G	2	Mouse	Leptin deficiency Hyperphagia and obesity (4 wk) Hyperglycemia and hyperinsulinemia (15 wk, following obesity) Insulin resistance and glucose intolerance Impaired diastolic function, mitochondrial energetic, Ca^{2+} homeostasis and cardiac efficiency Increased LV mass, fatty acid oxidation and lipid content	Advantages associated with mice reduced size (see text) Allows the evaluation of the early effects of obesity and insulin resistance on cardiac function and the effects of additional hyperglycemia at older ages	Certain degree of infertility Reduced metabolism and hypothermia	[118]
Pancreatectomy	S	1	All	Mild hyperglycemia No weight or insulin levels reduction	Useful for pancreatic regeneration studies Can be used in all animal model species Avoids pharmacologic toxicity of DM induction drugs Similar to type 2 DM due to pancreatic degeneration	Risk of infection Post-operative precautions Digestive complications	[186]
High-fat diet C57BL/6J	HFD	2	Mouse	Leptin and insulin resistance Hyperphagy and obesity Hyperglycemia and hyperinsulinemia (following obesity) Glucose intolerance Cardiac dysfunction (20 wk)	Advantages associated with mice reduced size (see text) Present many genetic and environmental features of the human disease High-fat diet C57BL/6J mice change myocardial substrate utilization prior to obesity and severe insulin resistance Useful for pharmacologic tests	Reduced metabolism and hypothermia Long high-fat diet period Mild hyperglycemia	[281]

G genetic model, *HFD* high-fat-diet model, *P* pharmacologic model, *S* surgical model, *wk* week

increased more rapidly during low-flow ischemia in the old hearts than in the adults. Again, training eliminated this age-associated difference in the response to ischemia, although it was not ascertained if the improvement was due to reversal of aging consequences or superimposition of some other effects. These findings indicate that in rats some age-associated changes in diastolic function are reversible and thus may not be intrinsic to aging but instead secondary to other processes, such as deconditioning [26].

Syrian cardiomyopathic hamster

The Syrian cardiomyopathic hamster is an established animal model for genetic cardiomyopathy, which has been extensively used since it was firstly described in 1962 by Homburger et al. [109]. They characterized an inbred line of Syrian hamster named BIO1.50 that experienced both cardiomyopathy and muscular dystrophy with 100% penetrance and [109] present an autosomal recessive mode of transmittance [109], thus being very useful for studying both cardiac and skeletal muscle disorders. Afterward, selective crossings gave rise to a new line, BIO14.6, which is now more widely used throughout the world [110]. Indeed, hitherto several cardiomyopathic hamsters (CM hamsters) have been derived from BIO14.6. Jasmin and colleagues established a new inbred line of UMX7.1 by cross-breeding BIO14.6 with unrelated healthy hamsters [126]. Later, another substrain of these hamster was isolated, the J2N [210]. The descendants of BIO14.6 and UMX7.1 were named as CHF146 and CHF147, respectively, and have been maintained at Canadian Hybrid Farms in Nova Scotia, Canada [113]. All the five CM hamsters (BIO14.6, UMX7.1, J2N, CHF146 and CHF147) develop an identical cardiomyopathy, progressing through prenecrotic, necrotic, hypertrophic and dilated stages [108]. Therefore, the disease progression in the hamster parallels the human genetic disease [66].

The most remarkable genetic manipulation of CM hamsters is the isolation of BIO53.58 from BIO14.6 [108]. Contrary to their forebears, BIO53.58 has a shorter life-expectancy and achieves much faster the disease endpoint of marked chamber dilation, which is common to all the CM hamsters, apparently without developing previous cardiac hypertrophy. Several descendants of BIO53.58, such as TO, TO-2 and MS200, were developed [180], and TO-2 is now maintained at Bio-Research Institute.

All the CM hamsters share the genomic deletion of about 30-kb interval, which includes the two promoters and first exons of delta-sarcoglycan gene with consequent loss of its protein product [212, 248, 249]. The consequences of the genetic loss of delta-sarcoglycan in heart are related not only to sarcolemmal fragility but also to coronary vasospasm from disruption of dystrophin-associated protein complex [44]. A genetic insult yet to be discovered was probably introduced during the isolation of BIO53.58 and has been inherited by its descendants, which could explain its distinct cardiomyopathy.

Pathophysiologically, two basic mechanisms contribute to cardiomyopathy in this model: (1) ischemic heart disease by vasospasm of the coronary circulation and (2) cardiomyocyte loss due to intrinsic cell defects [66]. Reports suggested that the vascular RAAS plays a critical role in the generation of increased coronary reactivity and resistance in young Syrian CM hamsters that have not yet developed the clinical manifestations of HF, being the increased reactivity due to endothelial dysfunction secondary to angiotensin-II-dependent oxidative stress [66]. Indeed, blockade of the RAAS during early stages of disease improves the clinical manifestations of dilated cardiomyopathy in this model [66]. With regard to cardiomyocyte loss, numerous studies showed autophagic vacuolar degeneration in cardiomyocytes, which could be improved by treatment with granulocyte colony-stimulating factor [288]. Another report provided novel evidence of a beneficial effect of vascular endothelial growth factor in the Syrian CM hamster via induction of myogenic growth factor production by skeletal muscle and mobilization of progenitor cells, which resulted in attenuation of cardiomyopathy and repair of the heart [328].

Moreover, the Syrian CM hamster has been shown to develop alterations in electrical and ionic homeostasis related to disruption of gap junctions, which contributes to arrhythmogenesis during the development of HF [247]. A recent report showed that adhesion junction precedes gap junction alterations and that angiotensin-II receptor blockade might be a new therapy for lethal ventricular arrhythmia by modulating both adhesion junctions and gap junctions remodeling [323].

In summary, several reports confirm that CM hamsters with genetic loss of delta-sarcoglycan recapitulate many pathophysiologic aspects of cardiac failure [39, 267, 296], but it is clear that despite its extended use, this model is far from being totally understood [247].

Genetically engineered rodent models

The development of molecular biology offers the opportunity to study the impact of overexpression or deletion of specific genes involved in the pathophysiology of CHF. Indeed, transgenic murine models will help understanding the molecular basis of CHF, which might open the door for the development of novel molecular targets for the treatment of CHF. A wide number of genetic modifications have been successfully introduced in mice, either in terms

of gain or loss of function. Besides the genetically engineered mouse models summarized in Table 2, other selective inbreed and other genetic animal models were presented in previous sections whenever appropriate.

General considerations

Besides ethical and philosophical questions, the use of animal models of HF needs careful consideration not only because the disease may be associated with discomfort and pain to the animal but also because results from animal studies are not readily transferable to human patients.

HF models were originally developed in rodents because of numerous potential advantages inherent to a small animal model. Housing and maintenance costs for rodents are much lower than for larger animals, thus allowing increasing the number of animals included in a given study and improving its statistical power. Moreover, recent technological advances in echocardiography, MRI and micromanometer conductance catheters have greatly upgraded the assessment of cardiac function in rodents, removing a significant barrier to their use in HF research.

The small size of mice presents some challenges in assessing myocardial function by conventional techniques (echocardiography, MRI), and the tenfold bigger myocardial mass of rats compared to mice gives the opportunity of performing more post-mortem histologic and biological analyses [223]. Nevertheless, cardiac physiologic assessments have been made easier by recent technologies such as ultrahigh resolution ultrasound [169] and micromanometer conductance for pressure–volume analyses [80, 218], but these techniques are quite expensive and pose a serious challenge to laboratories without an established expertise. The major advantage of mice compared to rats is the fact that pharmacologic studies become less expensive as the drug is usually administered proportionately to the animal weight. Moreover, mice are one of the most interesting research models to study the molecular basis of HF due to the availability of many genetically engineered strains made possible by their well-characterized genome and the easy introduction and stable transmission of gene mutations. Moreover, since 99% of the human genes have direct orthologs with mice, it is possible to generate transgenic mice models to mimic human disorders [71, 244]. Nevertheless, structural differences regarding human cardiovascular system represent another limitation of rodent models.

With regard to diastolic dysfunction, it should be emphasized that rodent models generally progress to SHF within a variable amount of time, which means in those animals DHF is only temporary step in the development of SHF. On the contrary, there are several human pathologies characterized by stable and isolated DHF, thus not evolving to systolic dysfunction. Therefore, small animal models could be misleading because they suggest that DHF invariably progress to SHF, which in fact seldom happens in humans. Additionally, in humans, DHF is a condition typically associated with aging, and the diastolic dysfunction/DHF animal models herein mentioned are relatively young.

Care should be taken when dealing with genetically engineered mice. Besides taking into account strain and gender issues [91, 272, 283], high levels of overexpression must be carefully interpreted. In fact, transgenic mice that express a biologically inert green fluorescent protein in a cardiomyocyte-specific fashion develop LV hypertrophy, dilation and systolic dysfunction in a manner directly related to the level of protein expression. Therefore, non-specific effects on LV structure and function may result from vast overexpression of even biologically inactive proteins [112]. Furthermore, certain phenotypes depend on the expression level of the gene concerned [43, 298], which means it is necessary to develop multiple transgenic lines to establish a gene-dosage effect. Development of compensatory mechanisms could be triggered in response to gene overexpression or deletion at a very early stage after manipulation, masking the direct effects of the targeted gene. The use of inducible and conditional gene activation or deactivation could be a good way of overcoming this problem [306]. In conclusion, despite the inherent pitfalls in transgenesis, many of them can be circumvented by creating additional transgenic lines that can be used as controls to check dosage or epigenetic sequelae, as has been recently reviewed [202]. A number of difficulties in interpreting a cardiac transgenic experiment can arise from the promoter that drives the transgene itself. For example, although the α-myosin heavy chain (α-MHC) promoter is often thought of as driving ventricular expression in the adult, its actual expression pattern is considerably more nuanced, with transient expression in the embryonic heart tube and atrial expression throughout development. If the experimenter is attempting to isolate events that occur as a result of expression only in the adult, more precise manipulation of transgene expression may be necessary to generate interpretable data. Inducible transgene expression allows precise and reversible expression of a normal or mutated protein that can be directed to a particular cell type at a particular developmental time. A number of drug-inducible systems have been described, but the tetracycline-based system is the most effective and widely used. However, like most tools, it must be used carefully as the tetracycline activator can, when expressed at high levels or for long periods of time, be cardiotoxic. Despite this concern, transactivator lines have been developed that show no cardiotoxicity for at least 6 months, and so these experimental limitations can be easily circumvented [250].

Table 2 Brief description of the most important genetically engineered mouse models used for heart failure research

	Gene		Mechanism	Structural changes	Functional changes	Comments
Cytoskeletal and sarcomeric proteins	Melusin [20]		Knockout	Cardiac chamber dilation and relative wall thinning	Depressed systolic function and myocardial contractility, pulmonary congestion and impaired adrenal responsiveness	Melusin is a muscle-specific integrin β1-interacting protein. Probably required for LV hypertrophy induced by biochemical stress but not by humoral stimulation
						No effect on cardiac structure or basal function in physiologic conditions or in response to angiotensin II or phenylephrine
						Leads to LV hypertrophy and favors the transition toward dilated cardiomyopathy and contractile dysfunction in response to chronic pressure overload
	Muscle LIM protein (MLP) [7]		Knockout	Myofiber disarray, severe LV hypertrophy, dilation and fibrosis	Systolic dysfunction and CHF Blunted response to β-agonist stimulation	Suitable model for long-term observation of drug effects on cardiac function and remodeling (near normal life span). Mutations in MLP were identified in patients with dilated or hypertrophic cardiomyopathy [199]
	Proteins linked to FHC (β-MHC, troponin T, MyBP-C) [176]		Knockout	These models are important to study the mechanisms linking the primary mutation and the secondary development of CHF. Moreover, environmental or genetic factors play a role in the development of each phenotype		
	Proteins linked to heritable dilated cardiomyopathy (actin, β-MHC, troponin T) [267]	Desmin	Knockout	Severe disorganization of muscle architecture associated with degeneration [192]		Mutation in β-crystallin (a molecular chaperone heat shock protein essential for cytoskeletal integrity) causes a desmin-related myopathy [303]
		Cardiac actin		Reduced number of actin filaments and myofiber disarray	Early post-natal death [145]	
		Dystrophin			Dilated cardiomyopathy only in the presence of concomitant urotrophin deficiency [86]	

Table 2 continued

	Gene		Mechanism	Structural changes	Functional changes	Comments
Neurohumoral receptors	Sympathetic nervous system	α1B-AR [3, 191]	Mutation	Ventricular hypertrophy increased ANF expression (sufficient for hypertrophy development)		Clinical studies with α1-AR selective blockers or activators of central α2-ARs have so far provided disappoint results [42] The activation of subtype-specific α2-AR at peripheral nerves has not been tried yet [306]
		α2A or α2C-AR [25]	Knockout		Faster progression to CHF and death when challenged with pressure overload (TAC) than wild-type or α2B knockout mice	Feedback presynaptic inhibition seems to be important to attenuate the detrimental effect of catecholamines
		β1-AR	Overexpression [63, 65]	Significant hypertrophy of the myocytes, altered nuclear morphology and concomitant fibrosis, with increased expression of apoptotic proteins in fibrotic areas	Elevated basal heart rate and increased contractility in young animals; at 35 weeks of age, the contractility decreases and many animals present clinical signs of HF and die before the age of 14 months. Contractile dysfunction is preceded by impaired Ca^{2+} handing [206]	Chronic activation clearly implicated in CHF development in both animal and clinical studies In a model with concomitant deletion of PLN gene, mice did not die prematurely anymore, the cardiac hypertrophy and fibrosis were inhibited, LV function was preserved and also the disturbed Ca^{2+} handling was restored These findings show that the β1-adrenoceptor–PLB-signaling cascade is a crucial regulator of cardiac contractility [64, 172]
		β2-AR	Overexpression [264]	Myocardial hypertrophy that could not be prevented [57, 265, 266]	Basal contractility; LV dP/dtmax, relaxation and heart rate were increased [14, 17, 59, 190]. The improved contractility could be attributed to better Ca^{2+} cycling of the SR, which showed decreased PLN expression [242, 326] Other studies showed that mice die earlier from severe HF indicated by cardiac dilation, pulmonary congestion and pleural effusion [58, 159]	In CHF, there is selective down-regulation of β1-AR and desensitization of both β1-AR and β2-AR (mediated by β-ARK1) Mice subjected to pressure overload through aortic constriction showed higher mortality and incidence of HF.
		β-ARK1 [140]	Knockout	Mice do not survive		
		β-ARK peptide inhibitor [140]	Overexpression		Increased cardiac contractility	Cross-breeding with cardiomyopathic MLP-knockout mice restores the responsiveness to β-agonist stimulation and enhances cardiac contractility [238] Cross-breeding with mice overexpressing calsequestrin enhances cardiac function and reduces mortality. Combination with the β-blocker metoprolol has an additive effect [95] β-ARK1 seems to be a putative therapeutic target

Table 2 continued

	Gene		Mechanism	Structural changes	Functional changes	Comments
Neurohumoral receptors	Renin-angiotensin system	AT-1 [221]	Overexpression	Significant cardiac hypertrophy and remodeling with increased expression of ANF and interstitial collagen deposition	CHF in the absence of blood pressure changes	This model attests the direct role of angiotensin II in cardiac hypertrophy
	Cytokines	TNF-α [143, 167]	Overexpression	Biventricular dilation, fibrosis, interstitial infiltrates and hypertrophy	Marked decline in cardiac function and blunted responsiveness to β-agonist stimulation	Clinical trials with TNF-α inhibitors failed to achieve beneficial results [181, 182]
		IL-6 and gp130 (receptor) [105, 106]	Overexpression	Ventricular hypertrophy	No progression to CHF	Gp130 signaling cascade could be a potential therapeutic target because of its cardioprotective effect
			Disruption	Myocardial apoptosis	Accelerated transition to CHF when subjected to pressure overload	
Cellular signaling proteins	Heterotrimeric G proteins	Gαq	Overexpression [47]	Cardiac hypertrophy with increased expression of ANF and β-MHC		Gαq signaling is necessary and sufficient to the development of cardiac hypertrophy
			Modest		Blunted response to β-agonist stimulation	Mice with attenuated hypertrophic response to pressure overload (expression of Gαq peptide inhibitor or lack of norepinephrine) have increased wall stress but no decline in cardiac function [67]
			High		Overt CHF	
			Transient expression of constitutively active Gαq [183]	Cardiac hypertrophy	Dilated cardiomyopathy	Gq signaling pathway could be an interesting therapeutic target to prevent cardiac hypertrophy and CHF
			Inhibition (overexpression of a dominant-negative Gαq) [2, 312]	Resistance to hypertrophy induced by pressure overload		
		Gαs	Modest overexpression [124]	Cardiomyopathy similar to that induced by chronic catecholamine administration in elderly mice (cellular degeneration, necrosis, replacement fibrosis…)		
		Gi	Conditional expression of Gi-coupled receptor ($R_0$1) [233]		High level of expression causes hyperactive Gi signaling with systolic dysfunction	It is still matter of controversy if up-regulation of Gi pathway is a compensatory response to hyperactive Gs signaling
					Suppression of $R_0$1 expression after 8 weeks prevents further myocardial degeneration and partially improves systolic function and CHF	

Table 2 continued

	Gene		Mechanism	Structural changes	Functional changes	Comments
Cellular signaling proteins	Small GTPases	Ras [114]	Ventricular expression of a constitutively active form	Hypertrophy	Diastolic dysfunction	
		RhoA [246]	Overexpression		Sinus and atrioventricular nodal dysfunction and contractile failure without ventricular hypertrophy	
		Rac1 [282]	Myocardial expression of constitutively active form	Transient hypertrophy seen among juvenile mice that resolves with age	Lethal dilated cardiomyopathy associated with neonatal activation of the transgene	
	Protein kinases	PKC-β2 [304]	Overexpression	Cardiac dilation and fibrosis	Reduced cardiac function	
		PKC-α [201]	Knockout		Less systolic dysfunction and LV dilation in response to LAD	Cardiomyocyte-specific expression of a PKC-α inhibitor leads to the same results of knockout [127]
		PKC-ε [286]	Overexpression	Mild concentric hypertrophy without fibrosis	Normal cardiac function	
		PKA [6]	Expression of catalytic subunit in heart		Dilated cardiomyopathy with arrhythmias and reduced cardiac function	Enhanced Ca^{2+} release from SR in response to β-AR signaling
		Calmodulin kinase II (CaMKII) [161]	Overexpression	Progressive LV hypertrophy and dilation	Overt CHF	CaMKII contributes to heart failure progression Expression of a cardiomyocyte-specific CaMKII inhibitory peptide reduces LV hypertrophy and dilation and systolic dysfunction [5]. A pharmacologic inhibitor of CaMKII (KN93) attenuated LV dilation and improved systolic function post-MI in wild-type rats, suggesting that this kinase could be a potential interesting therapeutic target [322]
		Calmodulin [90]	Overexpression	Myocardial hypertrophy	No CHF	Other downstream pathways of calmodulin signaling could prevent the progression to CHF
		Calcineurin [201]	Overexpression	Myocardial hypertrophy	CHF development within 2 months	

Table 2 continued

	Gene		Mechanism	Structural changes	Functional changes	Comments
Calcium-regulating proteins	L-type Ca^{2+} channels [209]		Overexpression	Ventricular hypertrophy, apoptosis and fibrosis.	Overt CHF within 8 months and death of CHF within 12 months in the majority of mice	
	Calsequestrin [128, 251]		Overexpression	Hypertrophy	Progressive CHF—increased SR Ca^{2+} storage and decreased systolic Ca^{2+} transients	Restoration of β-AR signaling improves cardiac function and reduces mortality in these mice [95]
	SERCA2A		Knockout [225]	Lethal in embryonic period	Impaired cardiac function	SERCA2a overexpression improves systolic function and contractile reserve in mice with aortic constriction [123]
			Heterozygous (null mutation) [225]		Enhanced cardiac relation and contractility	Restoring adequate levels of SERCA2A expression in failing hearts improves LV systolic function, remodeling and survival [297]
			Overexpression [9, 97]		Increased adrenergic drive and mildly reduced ventricular contractility at the age of 3 months; overt CHF and death with aging [49]	Mutation PLNR9C identified in inherited human cardiomyopathy and the phenotype can be reproduced in mice [261]
						PLN inhibition could be a potential therapeutic target, but it is not certain if the beneficial effect would be the same in all types of CHF
						Ablation of PLN in Gαq overexpressing and mutant MyBP-C expressing mice does not correct global cardiac dysfunction
						Studies in animal models similar to most common forms of CHF in humans are needed
			Knockout	Reverses cardiac remodeling and enhances cardiac function in mice overexpressing calsequestrin [252]	Increased contractility [170]	
					Preserves cardiac contractility and left ventricular chamber size close to normal in MLP-deficient mice [193]	
					Restoring expression of S100A1 to normal levels in post-MI rats improved LV function and reduced LV dilation	
	S100A1 [229]		Overexpression		Restoring expression of S100A1 to normal levels in post-MI rats improved LV function and reduced LV dilation	S100A1 is a calcium regulatory protein that facilitates calcium transport across sarcoplasmic reticulum by optimizing activity of ryanodine receptor and SERCA2A
	RyR [317]	FKBP12.6	Knockout	Cardiac hypertrophy	Disregulation of Ca^{2+} release in the myocytes	A benzothiazepine derivative JTV519 prevents the decrease of RyR2-bound FKBP12.6, improves cardiac function and avoids cardiac remodeling in a canine model of CHF raising the question of it could be a novel therapeutic target [321]

Table 2 continued

	Gene	Mechanism	Structural changes	Functional changes	Comments
ECM proteins	β1-integrin [269]	Knockout (cardiac selective)	Myocardial fibrosis	CHF	
	MMP-2 [96]	Knockout	Decreased LV dilation and rupture	Better cardiac function and survival rate in mice subjected to LAD ligation.	
	MMP-9 [61]	Knockout	Reduced LV dilation and collagen accumulation following LAD occlusion.		
	TIMP-1 [45]	Knockout	Increased LV remodeling after MI		
Oxidative stress	Mn-SOD [117, 271]	Tissue-specific conditional knockout	Dilated cardiomyopathy with fibrosis at 4 months of age	Reduced contractility	Molecular defects in mitochondrial respiration suggested that administration of antioxidants could restore cardiac contractility

AR adrenergic receptor, *ANF* atrial natriuretic factor, *PLN* phospholamban, *SR* sarcoplasmatic reticulum, *AT-1* angiotensin receptor 1, *β-MHC* β-myosin heavy chain, *MyBP-C* myosin binding protein-C, *PKA* protein kinase A, *PKC* protein kinase C, *RyR* ryanodine receptor, *ECM* extracellular matrix, *MMP* matrix metalloproteinase, *TIMP* tissue inhibitor of metalloproteinase, *Mn-SOD* manganese superoxide dismutase

Gene targeting has often been heralded as being more precise and useful than transgenesis. When coupled with tissue- or cell type–specific methodologies via Cre-lox technology, gene targeting offers a precise way of introducing specific mutations that will only be expressed in a defined cell type at a particular developmental time. Nonetheless, the continuous expression of the Cre recombinase system has been shown to cause decreased growth, cytopathic effects and chromosomal aberrations in cultured cells lacking exogenous lox sites [260, 275]. A self-excising retroviral vector that incorporates a negative feedback loop to limit the duration and intensity of Cre expression can avoid measurable toxicity, while retaining the ability to excise a target sequence flanked by lox sites, thus providing the basis of a less toxic strategy for the use of Cre or similar recombinases [275]. As is the case for transgenesis, the more precisely the targeting event can be manipulated, the more straightforward the data interpretation will be. In the heart, this is accomplished by rendering the targeting event cardiomyocyte specific via controlled Cre expression using a cardiomyocyte-specific promoter or even making cardiomyocyte-specific Cre expression inducible [277]. However, several reports have noted some cardiac toxicity due to high levels of Cre expression with the α-MHC promoter, especially in later adulthood [202]. One putative solution is to design the experiment such that the data are obtained before cardiac function and biochemistry are affected, circumventing any negative effect of Cre expression. More importantly, employing Cre-only transgenic mice in the same genetic background as part of the overall experimental design is absolutely necessary for proper data interpretation and to ascertain any potential effect of Cre alone. Alternatively, different cardiac Cre transgenes may be used. Moreover, tamoxifen administration only in the presence of the α-MHC-MerCreMer transgene produces a temporary reduction in cardiac function with some ventricular dilation, although this phenotype resolves in 7–14 days after tamoxifen administration [202]. Thus, if the MerCreMer transgene is used to inducibly delete a gene from the heart, controls that only contain this transgene with tamoxifen are critical.

Another drawback of rodent models is that many protocols have a sudden onset of HF due to a surgical or drug intervention, whereas human HF generally develops over a period of several years. Most models also use young adult animals, while human patients are usually old. In addition, human HF is often associated with atherosclerosis, hypertension, diabetes or obesity, but the development of atherosclerosis is rather rare in most rodent strains [92].

In addition, even though rodent models have been extremely useful in developing concepts concerning the pathogenesis of heart failure, apart from the Pfeffer's model [228], which predicted the utility of ACE inhibitors

in post-infarction [227], they have not predicted outcomes in phase III clinical trials. Although translation of findings to clinical trials requires preclinical studies where the appropriate animal model is used for either acute or chronic HF, therapeutic results obtained in small animal models are not necessarily predictive of outcomes in human patients but can provide a potential future approach in the human context. In this regard, two recent examples could be mentioned. Inhibitors of enzymes in the PDE5 family have been used to raise cGMP content in cardiac muscle in animal models of pressure overload, chronic β-adrenergic receptor stimulation, ischemic injury and doxorubicin toxicity showing antihypertrophic and cardioprotective actions. However, recent experimental results raise some question regarding the applicability of these findings to humans, in whose hearts PDE5 is present at much lower levels than those seen in animal models, and raise the possibility of PDE1, a dual-specificity phosphodiesterase present at high levels in human myocardium, as an alternative target for inotropic and cardioprotective actions [205]. On the other hand, despite the evidence for inflammatory activation as an important pathway in disease progression in chronic HF and the promising results of 'anti-inflammatory' therapies (such as antitumor necrosis factor-α approaches) in rodent models [146], clinical trials have hitherto failed to show benefit in HF patients [101]. The discrepancy between clinical and basic research findings could be explained by the inherent physiologic differences between humans and rodents in terms of pharmacokinetics and pharmacogenetics. On the other hand, several authors reinforce the importance of refining patient selection in order to optimize the benefits of new HF drugs [101, 174].

Finally, the majority of the numerous genetic studies performed in mice have not resulted in clinically approved treatment in humans thus far [202]. However, it is not uncommon for a drug to take over 20 years from inception to clinical application. Given that genetically modified mouse models have only recently become a mainstay approach, it may take many more years before approaches based on this technology are introduced into clinical practice.

Conclusion

The use of small animal models has proven to be an extremely valuable tool in understanding the pathophysiology of complex cardiovascular diseases like CHF. Due to the recent development of invasive and non-invasive techniques to evaluate hemodynamics in human patients, animal models of HF are becoming less important to study hemodynamics, neurohumoral activation and myocardial function. Furthermore, with cardiac transplantation surgery, end-stage human myocardium become available for molecular and biochemical studies. Nevertheless, animal models remain critically important to study myocardial changes during compensated, initial stages of CHF, during transition from hypertrophy to failure and during the process of remodeling, all of which are currently difficult or even impossible to follow serially in human patients. Animal models may also be relevant to study the effects of new pharmacologic interventions on hemodynamics, neurohumoral activation and survival under preclinical conditions.

At present, transgenic models of CHF are essential for understanding the molecular alterations underlying the development of the disease, as they allow the identification of genes that are causative for HF and to characterize molecular mechanisms responsible for the development and progression of the disease.

Finally, animal models that mimic distinct features of human HF will play an important role in unraveling the consequences of gene transfer and molecular techniques to correct disturbed subcellular processes in the failing heart. These experiments are indispensable, and these rodent models will continue to held an important role, not only in expanding our knowledge about the mechanisms underlying HF, but also in developing novel therapeutic strategies for CHF.

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