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Modeling heart failure in animal models for novel drug discovery and development

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Abstract

Introduction: When investigating drugs that treat heart diseases, it is critical when choosing an animal model for said model to produce data that is translatable to the human patient population, while keeping in mind the principles of reduction, refinement, and replacement of the animal model in the research.

Areas covered: In this review, the authors focus on mammalian models developed to study the impact of drug treatments on human heart failure. Furthermore, the authors address human patient variability and animal model invariability as well as the considerations that need to be made regarding choice of species. Finally, the authors discuss some of the most common models for the two most prominent human heart failure etiologies; increased load on the heart and myocardial ischemia.

Expert opinion: In the authors' opinion, the data generated by drug studies is often heavily impacted by the choice of species, and the physiologically relevant conditions under which the data is collected. Approaches that use multiple models and are not restricted to small rodents but involve some verification on larger mammals or on human myocardium, are needed to advance drug discovery for the very large patient population that suffers from heart failure.

1. Introduction

Heart failure is still the leading cause of death in the westernized world¹. Animal models of heart failure have been developed to both help us understand the pathophysiology of this disease, as well as a vehicle to test treatment strategies². The end-stage failing human heart displays several hallmarks of contractile pathology. These include a slowing of the

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contractile and relaxation kinetics, and a blunting/flattening or even reversal of the normally positive force-frequency relationship (FFR), along with impaired frequency dependent acceleration of relaxation (FDAR). For the derangement of these two processes, FFR and FDAR, there are currently no effective treatments. The choice of an animal model is one of the most important study aspects, as it largely predetermines to what extent the results can be extrapolated to the human patient population. To aid investigators in the selection of an animal model, we will here focus on the most common disease etiologies that lead to heart failure, and on the most frequently used animal models that have been developed to study drug treatment of heart failure.

End-stage heart failure is more of a syndrome than it is a disease. Heart failure is the final stage of a long process that typically takes many years, if not over a decade, to reach³. A reduced cardiac output can manifest via reduced pumping ability, resulting in heart failure with reduced ejection fraction (HFrEF), or can manifest via reduced ventricular filling, which results in heart failure with preserved ejection fraction (HFpEF). The underlying etiology of heart failure is diverse; there are many pathological events or processes that can initiate the downward spiral of cardiac function during the development of heart failure. Ultimately, when end-stage failure is reached, a number of common symptoms manifest in the patients. Treatment of these symptoms does not cure heart failure. Most drug treatments can slow, or even nearly halt, the progression of disease, but they are typically not targeted against the underlying initial etiology. Treatment of the initial underlying etiology would provide a much better option and outcome, but unfortunately in the early stages of the progression of this disease patients do typically not experience noticeably symptoms. Thus, initially heart failure often goes undiagnosed for many years until the symptoms become evident. At, or near this end-stage, too many secondary and subsequent processes and changes have taken place in the heart and patient that the alleviation of the initial cause no longer provides a cure, and symptoms have to be treated.

Although there are many different etiologies that lead to heart failure, the vast majority of end-stage heart failure results from 1) elevated load on the heart and 2) lack of enough oxygen to the heart; ischemia. Etiologies based on the elevated load on the heart are in the majority of patients caused by chronic elevated blood pressure, but are also not uncommonly caused by valvular lesions. These underlying causes increase the load on the heart, and the heart has to work significantly harder to maintain the needed cardiac output. A significant chronic elevated workload, when left untreated, will over time lead to heart failure. Etiologies based on ischemia are typically caused by a narrowing of the coronary arteries due to plaque formation. When left untreated, a coronary artery can get blocked, and a portion of the myocardium no longer receives oxygen, and dies. When this occurs suddenly, the patient suffers a heart attack. However, it can also occur gradually, and functional tissue loss occurs without the signs of a heart attack. The loss of tissue due to lack of oxygen causes the rest of the heart to have to work harder to maintain cardiac output, contributing to the progression of heart failure.

2. Human patient variability and animal model invariability

The human patient population suffering from end-stage heart disease is extremely diverse. Humans have a highly diverse genetic background, and even those with an identical genetic background experience different conditions throughout life that can modify their cardiac condition and progression of pathology. Ultimately, no two human hearts are identical, and they can react vastly different to a given pathological condition, as well as react differently to treatment of a pathological condition⁴. Unfortunately, this biological variability is virtually impossible to incorporate into an animal model. With very few exceptions (mainly in large animal models), animal models typically use inbred animals where all animals have a genetically identical background, with a highly similar and controlled living environment. Virtually all variability factors are tightly controlled and minimized/eliminated, so as to be able to interpret any change in an outcome parameter in regards to the intervention done. As such, a drug intervention or genetic intervention in an animal model reflects the response in that given model. The same intervention in a different animal strain may result in a different outcome⁵. In addition, differences in for instance murine strains are well documented for many aspects such as heart weight, heart rate, and blood pressure^{6, 7}, and in one of our own past studies⁸ we observed different responses to sub-physiological conditions in several commonly studied murine strains. Still, many strains within a species will react quite similarly to a given intervention, allowing for the interpretation of results beyond a specific strain within a species.

3. Consideration of species

One of the most critical points in choosing or developing an animal model of heart failure is the choice of species. The choice of species is typically not solely based on science factors alone, but often on other factors, including cost and duration of the study². The closer a species is to human regarding the biological factors under investigation, the less ambiguous it is to extrapolate the resulting data to the potential impact on humans. Generally, the closer the species size is to the size of humans, the closer many aspects of cardiac function are to human. Studies on pigs, dogs, and sheep are generally quite straightforward to extrapolate to humans, but studying these species is not only costly due to housing and duration of experiments, these species are also much harder and costlier to genetically manipulate. With a short gestation time, and a short time to adulthood, small mammals can generate several generations in a year, whereas in larger mammals, it takes multiple years per generation. Since genetic manipulation typically takes several generations to create, the currently most realistic option for genetic models are smaller mammals⁹. Thus, depending on the scientific question asked, if a genetic manipulation is deemed essential, larger species are typically not considered. In between the larger species (pig, dog, sheep) and mice are several other species that are considered. The rat, guinea-pig, and hamster are ~10 times larger than a mouse, while rabbits are ~10 times larger than a rat, and humans are another 10–25 times larger than an adult rabbit. Roughly, based on body weight the mouse is ~3 log steps removed from human, while the rat (and also hamster) is ~2 log steps removed, and the rabbit ~1 log step removed. Since the heart rate is roughly proportional to the log of the species' weight; the rabbit may be as close to human in that regard, as mice are to rats.

Heart rate is a long-known critical factor in the function of the heart. Many processes are significantly different in various species because they have to perform a specific task each heart beat, and the time to accomplish that task is widely different between small and larger mammals. With the resting cycle length in a mouse being only about 100 ms, and about 1000 ms in humans, this 10-fold difference in timing necessitates drastically different action potentials, EC-coupling (excitation-contraction coupling) characteristics, and drastically different myofilament kinetics¹⁰. For action potentials, the mouse has an extremely brief action potential, without the plateau phase that is very prominent in the human¹¹. To achieve this action potential shape, the mouse expresses an ion channel palette that is distinctly different from larger mammals. In addition, for EC-coupling the mouse almost exclusively relies on the sarcoplasmic reticulum (SR) to provide the activator calcium for the myofilaments, only a very few % of the calcium transient is derived from trans-membrane calcium handling (L-type calcium channel, and reverse mode sodium-calcium exchange)¹². In humans, this trans-membrane component is ~10 times greater and thus the SR contribution significantly smaller. In fact, studies showed that pharmacological blockade of the SR calcium handling process in the small rodent has a major impact on cardiac contractile properties, but in rabbits and humans, contractile function is barely impaired when the SR calcium handling is completely absent^{13, 14}. In addition, the kinetics of the contraction are ~10 times faster in a mouse at rest compared to a human at rest¹⁵. With a ~10 times faster action potential, and a drastically different EC-coupling, the myofilaments too have to be able to achieve this very short cycle length. To achieve this short cycle length/high heart rate, the mouse has different myofilament protein isoforms. The most prominent difference is the fast alpha-myosin heavy chain isoform that is expressed in mice, where human almost exclusively express the much slower beta-myosin isoform¹⁶. For species in between mice and humans, the change in action potentials, EC-coupling, and myofilament isoforms lie somewhere in between those of the mouse and human². Since these processes within a species all need to be in tune to achieve the heart rate prevalent to that species, all of these processes become typically more “human-like” as heart rate/size is closer to human¹⁵. One of the most critical functional differences to illustrate this is the force-frequency relationship. When heart rate elevates, force of myocardial tissue contraction increases very substantially in humans^{4, 17, 18} and dogs, somewhat less in rabbit¹⁹, even less in rats^{20, 21}, and this relationship is virtually absent in the mouse⁸.

Cardiac output is regulated to match oxygen demand with a sufficiently appropriate supply. There is a distinct species dependency on the range of oxygen consumption, and thus a distinct range of cardiac output demand. Cardiac output is the product of stroke volume and heart rate. Mathematically speaking, stroke volume regulation is typically minimal, and thus the cardiac output is mainly dictated by the heart rate. In the mouse, the range of the heart rate *in vivo* is rather narrow, ranging from roughly 600–700 bpm at rest to ~700–800 bpm at maximal exercise, representing an increase in cardiac output by ~20–25%. In humans, this increase is at ~10-fold larger; during maximal exercise cardiac output easily triples, i.e. increases by 200%–250%¹⁵. Thus, in humans a much wider range is achieved, and this necessitates regulatory systems that control and adapt cardiac output much more dramatically than in the mouse. Again, all of these processes typically become more “human-like” as heart rate/size of a species is closer to human. In heart failure,

phenotypically manifestation of the syndrome is most often observed under conditions where cardiac output needs increased⁴. Exercise intolerance is the most typical hallmark of heart failure, and thus the regulatory mechanisms that impact on cardiac output are of great importance to cardiac function¹⁷. However, the smaller the mammal, the lesser these regulatory mechanisms (including the force-frequency relationship, and maintenance/increase of stroke volume with heart rate) are present, the more they may providing a hurdle to extrapolation of findings to the human patient population^{9, 15}. An additional factor to be considered is the amount of sample provided by an animal. A human or dog heart will render several 100's of grams of material that can be studied, whereas in the mouse, hearts from multiple animals sometimes sometime have to be pooled to provide a single analyzable sample.

4. Animal models for overload-induced heart failure

When the heart has to work chronically harder to achieve the needed cardiac output, it eventually will go into failure. There are several underlying causes of load-induced heart failure, the most common ones being chronic hypertension, and diseases of the (aortic) valve. The latter causes either an obstruction to blood-flow, or an incomplete closing of the valve. In this area of research, many animal models have been developed that have greatly contributed to our understanding of load-induced pathophysiology of the heart, with details of these models given below.

The positive aspect of animal models of chronic hypertension is that most of these can be employed in various species. Several main types of models are employed (see table 1 for summary), the first category based on a surgical intervention that causes hypertension, a second set of models that are based on a chemically-induced hypertension, a third based on over-pacing the heart, and a fourth set are based on genetic manipulation. In surgically-induced hypertension, a non-compliant band is placed, typically around the aorta that causes the afterload on the heart to increase²². In most animal models an immediate constriction is employed where the lumen of the aorta is significantly reduced, causing an immediate increase in afterload. This sets in motion a remodeling process that ultimately can lead to the development of heart failure. The benefit of this intervention is that it is relatively cheap and quick, but the downside is its' immediate nature; the nearly instantaneous elevation of blood pressure does not mimic the more gradual development of hypertension that in humans develops over many years, or even over a decade. In other models a band is placed around the aorta (or pulmonary artery for right-ventricular outflow constriction) and gradually constrict this, but tightening the band in multiple steps, over a longer time period, causing a more gradually developing afterload that better mimics the human patient situation, but is generally more costly. Alternatively, a band can be placed around the aorta in a younger animal, and when the animal grows, the band causes a gradual increase in afterload²³. This model too better mimics the human patient situation, but also comes at the cost of keeping the animal for prolonged time until they grow into this constriction that eventually causes heart failure. Where placing a band around the aorta initially causes left-ventricular dysfunction, a band placed around the pulmonary artery instead will initially cause right-ventricular dysfunction, allowing for the investigation of different etiologies^{19, 24}. Caution should be taken in comparing models, and often in between animals, as a small variation in

constriction can lead to a large difference in overload, while right and left-ventricular processes in relation to increased afterload also often differ.

Models of pressure or volume overload can also be induced by manipulation of the valves. Surgical removal of a part of the valve or tendineae can result in a volume overload model, where each beat some blood flows back into the ventricle from the aorta²⁵. This volume overload overworks the heart, and causes the heart to further progress towards end-stage heart failure. Alternatively, stenosis of a valve can lead to a high transvalvular pressure gradient, resulting in a pressure overload of the heart, which in turn can lead to heart failure. This model is however typically restricted to mice, and even highly dependent on the strain of mice²⁶. Another surgical intervention is the implantation of a pacemaker that paces the heart at a high heart rate. These pacing-induced models are typically restricted to larger mammals, as they necessitate implantation of a (often for humans developed-) pacemaker^{27–29}. Since this pacemaker can typically be turned off, this model allows for easy recovery studies, or studies with different duration/intensity of pacing.

An alternative to the surgical intervention to increase the workload on the heart is the induction of hypertension by chemical intervention. For instance, as a model of mainly right ventricular overload, injection of monocrotaline, an alkaloid, induces pathological changes in the pulmonary vasculature and causes pulmonary artery hypertension and right ventricular hypertrophy^{30, 31}. This model is most commonly used in rats. Overstimulation of the beta-adrenergic system also can lead to heart failure. Administration of isoproterenol or dobutamine can increase the stress on the heart, initiating the downward spiral of the heart into heart failure^{32, 33}. Angiotensin-II is a strong vasoconstrictor, and several studies have verified its role in inducing hypertension and heart failure in different animal models, including rodents and dogs^{34–37}. Even though induction of hypertension could increase the workload on the heart leading to heart failure, lack of correlation between hypertension and cardiac dysfunction could occur in some models such as with the induction of the thyroid system. Administration of sodium-L-thyroxine induced cardiac left-ventricular hypertrophy and associated cardiac dysfunction, which was either not or only partially dependent on hemodynamic changes (e.g. increased blood pressure)^{38–40}. Not only that, but also the variation in mouse species, sex, and age between these experiments⁴¹ and others⁴² obviously signifies that cardiac alterations following experimental hyperthyroidism appear to be model-dependent and need to be cautiously clarified⁴¹. Overall, chemically-induced models are generally acute, and do typically not mimic well the more gradual development of overload as occurs in the patient population. Still, these models develop some of the phenotypical hallmarks of heart failure, and thus allow the model to be used to test drugs that alleviate these symptoms.

Another option to raise the heart's overload is to induce hypertension via genetic manipulation. A well-known model of genetic hypertension is the spontaneous hypertensive rat, in which cardiac performance starts to deteriorate at 20 months of age⁴³. This is an often used model to imitate hypertension-triggered heart failure in human as well as to investigate the shift from cardiac remodeling to failure^{44, 45}. Transgenic rats expressing a dominant-negative mutant of the natriuretic peptide receptor B was also explored to exhibit blood pressure-independent left ventricular hypertrophy that is increased by chronic volume

overload inducing heart failure⁴⁶. In mice, our own labs have revealed that vascular remodeling–associated hypertension leads to left ventricular hypertrophy and contractile dysfunction in the profilin-1 transgenic mouse model⁴⁷. Genetic manipulation of small animal models seems to provide a unique opportunity to study the pathophysiology and prospective pharmacological goals for treatment of heart failure.

5. Animal models for ischemic heart failure

When blood flow to (a part of) the myocardium is decreased, or is altogether halted because of a coronary obstruction, ischemia/anoxia occurs. Lack of sufficient blood flow to the myocardium itself is a major cause of heart failure^{48, 49}. Myocardial ischemia is linked to remodeling of left ventricle that starts out to be initially adaptive, but its persistence eventually hastens the progression towards heart failure. The reasons for this harmful transition from adaptive to maladaptive cardiac performance is not completely understood and has been reported to be impacted by extracellular matrix changes, neurohormonal axis, and/or the remaining myocardium loading conditions^{50–52}. Recently, work from our labs has shown that under baseline conditions, kinetics (but not force development) are impaired in right ventricular myocardium from human hearts in end-stage failure, with a more prominent slowing down of kinetics in myocardium from hearts with a primary ischemic failing etiology⁴. In order to imitate the heart failure progression in humans with coronary disease, several animal models have been developed⁵³ and potentially could help to identify the pathway/mechanism(s) involved in the pathophysiology of ischemic human hearts. Most of these experimental approaches can be employed in various species based on the surgical technique that is used for the induction of myocardial ischemia/infarction. Main types of models are employed (see Table 2 for a summary) are the coronary artery ligation, the second is the coronary artery embolization, third is the hydraulic occluder or ameroid ring constrictor, and fourth being cryoinjury models. These interventions are generally used to constrict and/or occlude coronary vessels and these occlusions can be done singly or in stages and acutely or chronically so as to trigger acute or chronic heart failure^{53, 54}. In coronary artery ligation models most often the left coronary artery is getting ligated or heat cauterized, and the thorax then closed⁵⁵. This intervention is the most commonly used to induce heart failure in animals from mouse to pig^{55–58}. Despite its widespread use, there are significant downsides in this intervention, including 1) nearly all case infarctions are relatively small (left ventricle average ~ 21%), and merely slight hemodynamic defects were shown typically due to a high sub-pericardial collaterals number in some species like dogs, and 3) more than 50% mortality rate caused by deleterious ventricular tachycardia^{59, 60}. In a different version of these models, a significant modification has been done by providing a temporary occlusion that is reported to imitate human ischemia/reperfusion injury⁶¹. Here, a temporary occlusion followed up with reperfusion permits flow recovery in the coronary artery bed that was occluded before⁶¹.

An additional intervention to induce the myocardial ischemia/infarction is the coronary artery embolization. Intracoronary embolizations with microspheres⁶⁵, beads of agarose/polystyrene or the thrombin and autogenous blood with fibrinogen intracoronary injection can be used⁶⁶. Around ~7 embolization processes are separately completed within 1–3 weeks in closed-chest dogs. After 3 months from the final microembolization, clinical heart

failure signs observed in human such as neurohumoral activation, dilatation of the left ventricle, and reduced ejection fraction, started to appear⁶⁵. This model is typically applied only on large animals, mostly in dogs and sheep, to induce heart failure^{65–68}. Benefits of this model are 1) the low risk of serious inflammatory complications due to percutaneous induction of coronary artery embolizations compared to surgical interventions such as thoracotomy, and 2) this model simulates the clinical situation in global ischemic cardiomyopathy, acute coronary syndrome and heart failure patients due to embolization of atherosclerotic and thrombotic debris into the coronary microcirculation. In general, this model can be used to study innovative pharmacological targets and surgical remedies for heart failure treatment^{59, 69, 70}. On the other hand, downsides are the complexity to manage the precise length and site of coronary artery occlusion, the repetitive microembolization sessions that could trigger malignant dysrhythmias that could be an attrition source, and difficulty in biological response interpretations due to myocardial response heterogeneity and diversity to the microembolization^{59, 65, 70}.

Another intervention to induce myocardial ischemia/infarction involve the use of the hydraulic occluder or the ameroid ring constrictor. Procedures start with thoracotomy of the left anterolateral followed by a pericardium incision, while a left coronary artery branch is uncovered and the hydraulic occluder placement. Then, the occluder is inflated in order to induce either partial stenosis or complete occlusion. To manage the occlusion degree and record the flow of downstream through the left coronary artery, an ultrasonic flow probe is positioned distal to the occluder⁷¹. In a similar way, an ameroid ring constrictor is implanted, yet occlusion is achieved in a different way. Due to the material's hygroscopic property, the casein plastic ring around the vessel will gradually narrow at body temperature^{59, 72, 73}. These interventions permit for controlled complete or partial coronary artery branch occlusions. Thus, they are appropriate to trigger heart failure, mainly in large animals, such as pigs^{72, 73} in a gradual manner, as often occurring in humans. A further factor in the choice of model is that the coronary variability and existence of collateral vessel networks is substantially different between species. For instance, the collateral network in pigs is very limited, when compared to dogs, and may be a limiting factor in the usefulness of the pig as a model of ischemic heart disease⁷⁴. In addition, the type of anaesthesia is to be considered when choosing a model, as it may influence ischaemia and reperfusion.

Cryoinjury is another model that can be used to study myocardial ischemia. Often used for mice⁶² and zebrafish⁶³, this model can be employed in larger mammals, such as the pig⁶⁴. The cryoinjury model is reproducible, and often display only a modest adverse remodeling, possible by representative of infarcts observed in the clinic⁶², but with the same drawbacks as many other surgical models, in that they are rather acute, than occur over time as in the general patients with myocardial ischemia.

In conclusion, there are a large number of animal models that allow us to study the impact of a drug in the area of heart failure. The advantages of a model need to be carefully weighed against the disadvantages, and realistically this critical decision also includes non-scientific factors, such as cost, effort, and time to complete a study. Ideally, more than one model is used, while keeping in mind that species that have cardiac regulatory mechanisms most

similar to human, are typically closer to a human in their size, with all their inherent disadvantages.

6. Expert Opinion

The complex nature of the dynamically beating heart is impacted by not only the proteins and processes in the heart, but also by biophysical mechanical forces and electric currents that are dynamically changing and interacting during a heart beat⁷⁵. This complex nature can simply not be captured by *in vitro* cell models, necessitating the use of animal models. An enormous wealth of information has been gathered by studies using these animal models of heart failure. Despite the vast majority of animal models being used are small rodents, the vast majority of currently available drugs for heart failure patients have been developed by large animal models. Still, the trend towards using small rodent models is still increasing; cheap and fast is “winning”, with to a certain extent physiological relevance, rigor, and sound scientific premise often being collateral damage in the race to fund science. Large animals models take time to develop, and are costly. Studies on human tissue are hampered by infrequent availability, and long times to completion of studies. When these studies take several years, often more than 4–5 to complete, the typical funding mechanisms that are limited to 2–5 years are not adequate, as the study cannot deliver results in that time-frame. As a result, many scientists, knowing and acknowledging that larger animal models would render results more easily translatable to the human population, feel or are “forced” to switch to rodent models to conform with funding guidelines and reviewing practices/trends. On a regular basis, funding agencies hold workshops on these very issues (the relevance and need of large animal models and the study of human hearts), and resulting publications by the field-leading experts underline these needs to move the field forward⁷⁶. Unfortunately, the outcome of these expert workshops is not effectively put into practice regarding the funding climate; it remains set up for such proposed projects to be unfavorable due to their long completing time.

There is no doubt in our minds that murine models are very valuable (as we have used, generated, and studied many of these ourselves), specifically the genetic models that cannot be executed in large animals, but their limitations are too often minimized or neglected. For fundamental basic science questions, and questions related to signaling cascades and mechanistic understanding of biological interactions, these models are effective, as most of these studied processes are very similar between mice and humans. However, for drug studies in contractile heart failure, they are in almost all cases too remote from the human contractile kinetics to allow for meaningful interpretation of the data they provide. The fast heartbeat of the mouse is achieved by expressing different ion channels, qualitatively and quantitatively different EC coupling, and different motor protein isoforms, that are all tuned to work in concert for the heart to contract and relax over 10 times each second. In addition, regulatory mechanisms that can alter cardiac output are paramount in humans, but these mechanisms are almost non-existing in mice, since the mice barely changes cardiac output (only ~20–25%, compared to 200–250% or even more in humans). Human myocardial tissue studies have shown that there are 2 main pathological signatures in human end-stage heart failure: slowed contraction and relaxation kinetics at resting heart rate^{4, 77, 78} and the inability to increase contractile strength with elevated heart rate^{4, 17, 79}. The latter is very

critical, since impaired exercise capacity is typically the first symptom that causes a patient to be diagnosed with heart failure. This frequency-dependent behavior, or force-frequency relationship (FFR), is powerful in healthy humans and large mammals^{4, 17, 80}; contractile force is greatly enhanced when heart rate is increased, while frequency-dependent relaxation (FDAR) is greatly accelerated^{4, 17, 80}. As the species is smaller in size, the magnitude of the FFR and FDAR diminishes², and in the mouse these regulatory mechanisms are ~10 times less prominent, to the point where they are barely existing^{10, 15}. In fact, only under very tight physiological relevant conditions the FFR is still present/positive in mice²¹, many studies report a slight negative FFR, even in healthy mice in the physiological heart rate range^{8, 81, 82}. Thus studying FFR and FDAR, two processes centrally involved in both systolic and diastolic heart failure in mice leads to data that are largely irrelevant for human physiology or (treatment of) pathophysiology. With contractile function being the primary function of the heart, in our opinion, the vast majority of studies investigating drugs that are designed to impact on either electrical function, contractile function, and/or relaxation kinetics improvement are greatly hampered by the differences in species.

For many animal models, contractile functional assays are conducted *ex vivo* on cells, multicellular preparations, or whole hearts. These assays can easily be used to study the acute impact of a drug on contractile strength and kinetics of the contraction. In our lab, we use multicellular muscles from both failing and non-failing human hearts to study acute drug impact on contractile and kinetic function^{4, 14, 83}, as well as on arrhythmogenicity⁸⁴. The outcome of the experiments does not suffer from a species difference with patients, but the logistics of the procurement of live human tissue takes a significant and continuous effort, and the availability of such human hearts tissue is infrequent, often leading to a long study completion time. In addition, the inherent human variability often necessitates the use of large n-numbers, further prolonging project durations, up to 8 years for a recent study on contractile properties of human right ventricular tissue, using 80+ human hearts⁴. Luckily, testing acute drug impact is often done in a paired fashion (i.e. in absence and in presence of the drug in the same experiment), leading to a drastic reduction in n-numbers, and thus a reduction in completion duration. Possibly, iPSC can be used, after further development maturing process, to circumvent the scarceness of human tissue. Unfortunately, maturing of iPSC's so they fully look and behave like adult cardiomyocytes is not yet achieved.

There is no perfect animal model, not for any aspect of studying cardiovascular pathology. However, we urge to carefully consider that the data generated by the study of a drug is often heavily impacted by the species, and also the physiologically relevant conditions the data is collected. Approaches that use multiple models, and are not restricted to small rodents only but involve some verification on larger mammals or human myocardium, are needed to advance drug discovery for the very large patient population that suffers from heart failure.

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Highlights

- Animal model studies often use inbred strains that do not reflect the variability of the human patient population, limiting generalization of the study outcome to the overall patient population.
- One of the most common pathological signatures of human heart failure is the blunting or reversal of the force-frequency relationship, which is a regulatory mechanism predominantly used by larger species, but not by small species.
- The heart rate of a species critically is critically related to the underlying molecular composition of ion channels and contractile protein isoforms.
- Human heart failure developed in many etiologies over many years/decades. Models that provide a much faster onset of disease may not necessarily reflect on the human disease process and progression.
- Drug treatment of *ex vivo/in vitro* human heart myocardium allows for a more direct translation to the patient population, but those investigations are logistically challenging.

Table 1.

Models of overload-induced heart failure

Interventions	Benefit	Downside	Reference(s)
Surgically-induced hypertension <i>Pressure overload</i>	Cheap and quick	Poorly mimics the human situation	[22]
Acute Banding			
Gradual Banding	Mimics patient situation	More costly/labor intensive	[19, 23, 24]
<i>Volume overload</i>		Mortality and complication rates are high	[25, 26]
Mitral regurgitation			
Aortic regurgitation	Similar to the evolution occurring in humans		
Arteriovenous shunt			
Chemically-induced hypertension	Allow to test drugs that alleviate the phenotypical	Does not mimic the more	[30, 31]
Monocrotaline			
Isoproterenol or dobutamine	hallmarks of heart failure	gradual development overload in human patients	[32, 33]
Angiotensin-II			[34–37]
Pacing-Induced overload	Reversible, and slow progression can be achieved	Does not mimic human etiology	[27–29]
Genetic manipulation-induced hypertension			
Spontaneous hypertensive rats	Allow to study the pathophysiology	Could not typically represent	[43–45]
Profilin-1 transgenic mice	pharmacological goals for treatment of heart failure and prospective	the heart failure outlines in human	[47]

Table 2.

Models of ischemic heart failure

Interventions	Benefit	Downside	Reference(s)
Coronary artery ligation	Most commonly used to induce heart failure A significant modification through temporary occlusion to imitate human ischemia/reperfusion injury	Expensive and time-consuming Small infarctions and slight hemodynamic defects > 50% mortality rate (ventricular tachycardia)	[53–57] [58–60]
Coronary artery embolization	Low risk of serious inflammatory complications Simulates the clinical situation and study innovative pharmacological targets and surgical remedies for treatment of heart failure	Complexity to manage the precise length and site of coronary artery occlusion Trigger malignant dysrhythmias Difficulty in biological response interpretations	[62–66] [67]
Hydraulic occluder or ameroid ring constriction Cryoinjury	Widely used	Lacking of predictability relating to the functional stenosis degree	[61]
Modest adverse remodeling	Reproducible	Acute nature not always reflect human myocardial ischemia	[72–74]