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Editorial

Murine models for heart failure: Their creation and applicability to human still require critical and careful considerations

Heart failure (HF) remains a leading cause of morbidity and mortality worldwide. Given the high prevalence of risk factors like hypertension, diabetes mellitus, dyslipidemia or aging population, the number of patients with HF will further increase in the coming years. HF includes a spectrum of clinical phenotypes ranging from asymptomatic, stable to decompensated states that can finally involve left ventricular dilation, increased end-diastolic pressure and/or reduced cardiac output. HF has a high medical and socioeconomic burden, which necessitates an urgent improvement of current treatments and the need to develop new therapeutic strategies that prevent or even reverse the disease [1].

Animal models have greatly contributed to expand our insights into decisive pathomechanisms of diseases, the identification of new therapeutic targets and drug development [2,3]. Benefitting from available and emerging technologies of genome manipulation, rodent models were instrumental to dissect the individual aspects of the complex pathophysiology of HF. Genes can easily be overexpressed, depleted or manipulated. Mice and rats are sharing a high homology to the human genome, i.e. only about 1% of the human genes have no mouse orthologue and *vice versa*, making murine models suitable system to study human diseases despite the known differences in heart rate, calcium cycling, and action potential and contractile protein properties [4,5]. To recapitulate key aspects of human HF, numerous experimental models have been (and are being) established. Having in mind the myriad of underlying causes of HF in humans, of course, none of these animal models can perfectly recapitulate such complex human diseases. Thus, researchers need to carefully consider both the advantages and the limitations of the selected model that recapitulates usually only one key aspect of the disease being investigated [10].

A solid experimental design of an animal study needs to address many concerns such as randomization, power calculations for sample size estimation, standardization or blinding of researchers; in addition, the animal species, the strain, the experimental model, the dosing of drugs and the experimental read-out also need careful consideration. Although there is an increasing need to improve the experimental design to enhance reproducibility and translatability of preclinical studies [6], the intrinsic model requirements still need critical considerations to ensure proper and reliable conclusions.

In this journal, Patel and colleagues [7] have illustrated the optimization process of a rat model to monitor the transition process from compensatory left ventricular hypertrophy to decompensated HF. This pathomechanistic process of transition is most common to hypertensive heart disease [8]. To simulate hypertension and hypertension-associated increased left ventricular pressure, Patel *et al.* [7] employ two different surgical models of abdominal aortic banding [9] combined with different grades of aortic banding and time points. Such preliminary studies that optimize experimental conditions for certain clinical questions, recall the importance of the awareness of the correct choice of animal models [10].

In general, narrowing of the aorta is commonly used to induce left ventricular pressure overload in mice and rats to mimic adaptations of the heart observed in hypertensive patients or patients with aortic valve stenosis. These adaptations include the development of cardiac hypertrophy, a physiological mechanism to meet the functional demand of the cardiovascular system, compensated HF and the transition to decompensated HF. Usually, the human disease develops over many years and decades, while most animal models produce the pathology of interest over days to weeks [11–13]. There are several forms of aortic banding being applied, each of them having advantages and limitations that need a thoughtful consideration of the specific scientific question. In general, the outcome of aortic banding is variable with regards to the resulting phenotype, i.e. cardiac hypertrophy with or w/o progression to decompensated HF and/or the time course of HF progression, based on murine strains, sex, size of the needle used, size of aorta, tightness of ligature and positioning of the ligation. Of note, the severity of aortic constriction has the greatest impact on disease phenotype and should be carefully controlled [2,9,10,14–16]. In mice, the transverse aortic constriction (TAC) model developed by Rockman *et al.* is most commonly used to investigate the underlying mechanisms of cardiac hypertrophy or HF [16]. The hypertension onset in this model is sudden and causes an increase in LV mass of about 50% within two weeks, thus, this is the ideal model to investigate intervention strategies that affect the development of cardiac hypertrophy, although the time scale of HF development differs significantly from that in patients with hypertension or aortic stenosis [11]. Chronic left ventricular pressure overload resulting in cardiac hypertrophy and ultimately cardiac dysfunction can also be induced by abdominal aortic constriction (at the infrarenal and suprarenal position). In this model, the transition to HF is more gradual, making this model more relevant to hypertension-associated HF. The surgery can be performed more easily compared to TAC, without the need for chest opening or mechanical ventilation and is more often applied to rats [9].

Overall, for the replication of human HF, besides the time course of disease progression with slow evolving development of left

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ventricular hypertrophy, fibrosis, diastolic dysfunction and eventually systolic dysfunction in response to hypertension, the complex multifactorial pathogenesis of HF involving a large variety of comorbidities and varied age of the patients should be taken into account when selecting and designing an animal model. Certainly, no animal model can mirror all aspects leading to HF in humans. When selecting animal models, researchers should consider not only technical advantages and disadvantages such as costs, infrastructure and the requirement for specialized personnel to perform the experiments with maintained quality and reliability, but also the main purpose of the experiment. Despite the criticism that small animal models of HF are not perfectly recapitulating the human disease or physiology, they offer unique opportunities to dissect precise pathomechanisms, predisposing conditions and their (patho-)physiological outcome *in vivo* without confounding effects of comorbidities – opportunities that are limited to certain cellular readouts in human *in vitro* models. Further reinforcement of complementary approaches using human *in vitro* models (e.g. isolated cardiomyocytes, cardiac tissue or cardiomyocytes derived from induced pluripotent stem cells) and murine *in vivo* models will help to overcome many of the model specific limitations and foster translation of identified potential targets into a more clinical context.

Carefully designed, well-characterized and controlled animal models will remain indispensable tools for advancing the mechanistic understanding of human cardiovascular disease, for testing hypotheses at the organism level, complementing *in vitro* findings and the study of cause-effect relationship between clinical conditions and disease outcome.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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