event will heal, but the animal's heart will remodel itself in order to compensate for the loss of efficiency. In other words, the animal will develop HF type conditions that can be used to assess the efficacy of test compounds.[39] In practice, surgical induction of an ischemic event (and implantation of cardiovascular monitoring equipment) is followed by a recovery period (3–7 days). Dosing with test compounds is then initiated and cardiovascular function is monitored over a period of weeks to months in order to determine if the test compound is preventing progression into HF. Factors such as mean aortic pressure, contractility, and survival can be used as determinants of efficacy of test compounds relative to untreated animals.[40]

As an alternative, it is also possible to induce HF conditions using a rapid pacing protocol similar to that described for the creation of a model suitable for the study of atrial fibrillation. In the tachycardia-induced HF model, the application of a rapid pacing protocol is used to induce dilated cardiomyopathy (DCM) and left ventricle heart failure (LV HF). These conditions are characterized by LV dilation, an increase in the LV chamber radius to wall thickness ratio, and a resulting increase in LV wall stress. The physical remodeling of the heart is consistent with that observed in human HF. In addition, changes in the neurohormonal system that regulates cardiovascular function (e.g., the renin-angiotensin-aldosterone system) occur in this model in a time-dependent manner consistent with clinical observation. To date, this model has been successfully developed in dogs, pigs, and sheep for the study of HF progression and potential disease modifying therapies.[41]

In practice, the model is generated in a similar manner to the tachycardia-induced AF model. Surgical implantation of a pacemaker and electrical monitoring equipment is followed by a recovery period (2–3 weeks). Rapid pacing (approximately 220 beats per minute) is applied over an additional 2–3 weeks, and this leads to DCM and the associated LV HF described above. Unlike the tachycardia-induced AF model, however, burst pacing is not required for productive use of this model. Animal can be dosed with test compounds during the pacing period in order to assess their ability to slow remodeling of the heart. Efficacy can be determined by monitoring for changes in cardiovascular functions (e.g., contractility, LV ejection fraction, mean arterial pressure, LV systolic pressure, LV diastolic pressure, etc.) over time in the presence of test compounds. In addition, changes in concentration of circulating neurohormones (e.g., norepinephrine, atrial natriuretic peptide, aldosterone, etc.) and renin activity can be assessed via blood sampling. Finally, at the end of the study, myocytes can be isolated from test animals in order to determine the potential protective effect of test compounds. Once isolated, the myocytes can be studied structurally and biochemically to assess their overall health and contractility measurements provide additional insight regarding progression toward HF. Compounds capable of treating HF (suppressing disease progression) will show improvements in some, if not all of these areas.[42]