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Small and large animal models in cardiac contraction research: Advantages and disadvantages

Nima Milani-Nejad, Paul M.L. Janssen *

[a] Department of Physiology and Cell Biology and D. Davis Heart Lung Institute, College of Medicine, The Ohio State University, OH, USA

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ABSTRACT

The mammalian heart is responsible for not only pumping blood throughout the body but also adjusting this pumping activity quickly depending upon sudden changes in the metabolic demands of the body. For the most part, the human heart is capable of performing its duties without complications; however, throughout many decades of use, at some point this system encounters problems. Research into the heart's activities during healthy states and during adverse impacts that occur in disease states is necessary in order to strategize novel treatment options to ultimately prolong and improve patients' lives. Animal models are an important aspect of cardiac research where a variety of cardiac processes and therapeutic targets can be studied. However, there are differences between the heart of a human being and an animal and depending on the specific animal, these differences can become more pronounced and in certain cases limiting. There is no ideal animal model available for cardiac research, the use of each animal model is accompanied with its own set of advantages and disadvantages. In this review, we will discuss these advantages and disadvantages of commonly used laboratory animals including mouse, rat, rabbit, canine, swine, and sheep. Since the goal of cardiac research is to enhance our understanding of human health and disease and help improve clinical outcomes, we will also discuss the role of human cardiac tissue in cardiac research. This review will focus on the cardiac ventricular contractile and relaxation kinetics of humans and animal models in order to illustrate these differences.

Contents

Abbreviations: AAV, adeno-associated virus; APD, action potential duration; dF / dt_{max}, Maximal velocity of contraction in cardiac trabeculae; $(dF / dt_{max}) / F$, Maximal velocity of contraction divided by developed force in cardiac trabeculae; dF / dt_{min}, Maximal velocity of relaxation in cardiac trabeculae; $(dF / dt_{min}) / F$, Maximal velocity of relaxation divided by developed force in cardiac trabeculae; $LV\ dP / dt_{max}$, left ventricular maximal rate of pressure rise; $LV\ dP / dt_{min}$, left ventricular maximal rate of pressure decline; LVSP, left ventricular systolic pressure; LV τ, left ventricular isovolumic relaxation time constant; MHC, myosin heavy chain; NCX, sodium calcium exchanger; RT_{50}, Relaxation time 50%: Time from peak force to 50% relaxation in cardiac trabeculae; SERCA, sarcoplasmic-reticulum calcium ATPase; TTP, time to peak: time from stimulation to peak force in cardiac trabeculae.

* Corresponding author at: Department of Physiology and Cell Biology, The Ohio State University, 304 Hamilton Hall, 1645 Neil Avenue, Columbus, OH 43210-1218, USA. Tel.: 614 247 7838; fax: 614 292 4888.
E-mail address: janssen.10@osu.edu (P.M.L. Janssen).

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1. Introduction

According to a preliminary report by the National Vital and Statistics Reports, heart disease remains the number one cause of mortality in the United States, accounting for almost 600,000, or about a quarter of all, deaths in 2010 (Murphy et al., 2012). Our understanding of the cardiovascular system has greatly advanced in the past decades, however, further research is required in order to expand our knowledge and provide novel therapeutic avenues. Donated human hearts, either non-transplantable (ranging from healthy to diseased) or end-stage failing hearts typically obtained at time of transplantation, are a great tool for addressing this issue. These samples are however available in very limited quantities, and exhibit great variability due to differences in factors such as genetics, medications, diets, social habits, and diseases. There thus exists a need to have a suitable animal model where cardiovascular physiology and disease can be studied efficiently and reliably with potential translational applicability to humans.

The basic principles of cardiac excitation and contraction in all of the species discussed in this review are relatively conserved. The cardiac cycle sequence starts with the sino-atrial node depolarization which spreads to the atria causing their activation. After a brief pause at the atrio-ventricular node, the depolarization current spreads to the bundle of His, purkinje fiber system, and ultimately results in stimulation of ventricular myocardium. On a cellular level, depolarization along the cardiomyocyte T-tubules activates the voltage gated calcium ion channels, and this influx of calcium induces release of calcium from the sarcoplasmic reticulum. Calcium binding to troponin activates the myofilaments and permits cross-bridge cycling and cardiomyocyte shortening, resulting in pumping of blood from the ventricles into the pulmonary and systematic circulations. Relaxation process involves de-activation of the myofilaments and removal of cytoplasmic calcium mainly by the sarcoplasmic-reticulum calcium ATPase (SERCA) and sodium calcium exchanger (NCX) systems. This sequence is very rapid and occurs, depending on the species and heart rate, within tens of milliseconds in mice to a couple of hundred milliseconds in humans. This rapid and cyclic nature presents a significant obstacle in cardiac research. Membrane potential, ion concentrations, mechanical force, and modulation factors are never in equilibrium. Moreover, each of these factors constantly modulates each other. As a result, modulation of one factor typically impacts all other factors, and thus it is hard, if not impossible, to assess the specific impact of an intervention on one of these factors alone.

What is the single best animal model in the cardiac field that can be used in lieu of human hearts? One major concern in addressing this question is that the cardiovascular system of each animal has evolved differently in order to meet the demands of that species. The heart of a small animal such as mouse can easily beat up to 800 times per minute (Ostergaard et al., 2010), an elephant has a heart rate of only 35 bpm (Bartlett et al., 2009). Table 1 shows the inverse relationship between body weight and heart rate while blood pressure remains relatively constant across various laboratory animals and humans. In fact, the relationship between body weight and various cardiovascular parameters can be described with allometric equations such as heart weight (HW (g) = 6.0 × $BM^{0.98}$) and P–R interval (PR (ms) = 53 × $BM^{0.24}$) where BM is body mass in kg (Prothero, 1979; Noujaim et al., 2004). Hearts of smaller species need to contract and relax more rapidly than larger species in order to maintain cardiac output at high heart rates. This difference in cardiac contractile kinetics is highlighted in Fig. 1; ventricular muscles of various species were stimulated ex vivo at or slightly below their in vivo resting heart rates. The time it takes for contraction and relaxation varies between species due to differences such as excitation, calcium handling, and myofilament protein isoforms (Janssen & Periasamy, 2007). As a simple rule, the closer the heart or body weight of the animal model to human; the more similar are the hearts. Depending on the cardiovascular process being studied, the choice of animal model needs to be considered carefully since it affects experimental outcomes and whether findings of the study can be reasonably translated to humans.

As will be discussed later in detail, there is no perfect animal model of the human heart; each model has its own set of advantages and disadvantages. The purpose of this review is to provide an overview of the strengths and weaknesses of commonly used animal models including mouse, rat, rabbit, canine, pig, and sheep in cardiovascular research.

Table 1
Comparison of cardiovascular parameters of human and animal models.

Species	Body weight (kg)	Heart rate (bpm)	Systolic pressure (mm Hg)	Diastolic pressure (mm Hg)
Mouse	0.02–0.063	310–840	113–160	81–110
Rat	0.225–0.52	250–493	84–184	58–145
Rabbit	1–6	130–300	90–130	60–90
Canine	7–16	70–160	95–136	43–66
Sheep	20–160	60–120	91–116	102
Pig	200–300	50–116	135–150	–
Human	50–86	72	120	80

Lowest and highest values from multiple sources as summarized in Ostergaard et al. (2010).

2. Small rodent models (mouse and rat)

2.1. Advantages

The small rodent animal models, mouse and rat, have unique properties that make them valuable and indispensable to cardiac research. Although, as discussed below, there are very significant differences between small rodents and humans; the use of rodent

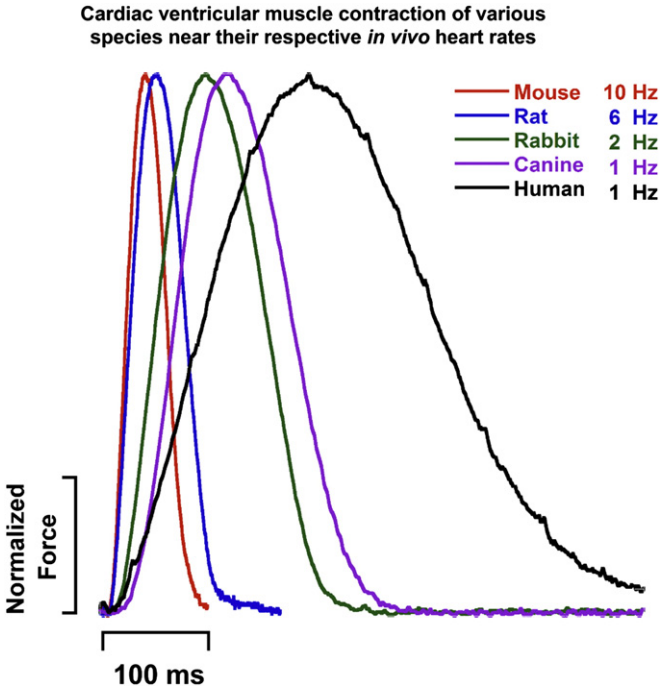

Fig. 1. Right ventricle muscles were stimulated ex vivo near the species' resting heart rates as indicated. For clarity purposes, only a single twitch of each species is shown. Temperature is 37 °C in all traces. Sources of tracings are as follows, mouse: C57BL/10 strain adapted from (Rafael-Fortney et al. (2011), rat: male LBNF-1 strain adapted from Monasky et al. (2007), rabbit: *unpublished data*, male New Zealand White rabbit, canine: mixed-breed canine adapted from Billman et al. (2010), Human: *unpublished data*, donor heart with abnormal ECG, borderline concentric left ventricular hypertrophy, mitral valve regurgitation, and ejection fraction of 55%.