The Giraffe as a Natural Animal Model for Resistance to Heart Failure with Preserved Ejection Fraction

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) is a leading form of human cardiovascular disease and commonly associated with systemic hypertension. Unique evolved adaptations in giraffe myocardia may be a natural animal model of resistance to HFpEF. In humans, pressure-overload induced left ventricular thickening (PLVT) impairs diastolic relaxation, elevates left atrial pressures and may progress to heart failure with symptoms including exercise intolerance. In healthy giraffe, the left ventricle thickens as developmental neck lengthening widens the vertical distance between the heart and head increasing pressures needed to maintain constant brain perfusion. Yet, diastolic relaxation and exercise capacity are unimpaired, a critical adaptation for prey species such as giraffe. The proximate mechanisms underlying this unique cardiovascular physiology are not yet characterized. Developmental PLVT in giraffe emerges as a species-specific evolved adaptation which offers a roadmap for identifying innovations in therapeutic and prevention strategies for HFpEF.

INTRODUCTION

Bioinspired strategies have sparked a rapidly growing list of diagnostic and therapeutic applications including wound healing, anticoagulation, infection control and biomedical imaging [1-4]. However, there have been few efforts to apply bioinspired approaches to human heart disease, especially heart failure. The purpose of this review is to: 1) define the unique cardiovascular adaptations of the modern giraffe as a potential natural animal model of resistance to heart failure with preserved ejection fraction (HPpEF) and 2) demonstrate how expanded physician awareness in comparative animal physiology can serve to inspire innovations to solve complex clinical human pathophysiology.

Heart Failure with Preserved Ejection Fraction (HFpEF)

Cardiovascular disease (CVD) is the leading cause of death in the United States, killing a person every 37 seconds [5]. Heart failure (HF), a chronic progressive form of CVD, is characterized by the heart’s inability to pump sufficient blood to meet needs and requirements of the body. Among patients over 65 years of age in the US, it is the leading reason for hospitalization and its prevalence around the world is increasing to due to an aging population [6-8]. Heart failure is commonly classified based on whether the left ventricular ejection fraction (EF) is in a normal range, borderline, or reduced [9]. Advances in both pharmacologic and device-based therapies over the past four decades have significantly lowered mortality and morbidity in patients with reduced left ventricular EF [10]. Yet, despite significant research investment, similar progress has yet to be accomplished in the treatment of heart failure with preserved ejection fraction (HFpEF), commonly referred to as “diastolic heart failure”. The human costs are high: HFpEF accounts for half of all heart failure diagnoses and has an estimated five-year survival rate of only 35% [11]. While multiple conditions including obesity, coronary artery disease, diabetes, and chronic kidney disease are associated with HFpEF, systemic hypertension is one of the most common and presumably contributing factors [12].

Arterial hypertension follows Ohm’s law for fluids as a response to pathologically increased arterial resistance in order to maintain cardiac output. However, increasing afterload imposes a greater workload on the left ventricular myocardium leading to hypertrophic changes. Progression to heart failure syndromes in parallel with other problems that include stroke, arterial disease, coronary events, and general cardiovascular mortality often follow [13]. Hypertension has reached epidemic
proportions over the past three decades. Given its connection to left ventricular hypertrophy (LVH), it is not surprising that HFpEF has emerged as the fastest growing form of human heart failure [14].

**Pathological PLVH (Left Ventricular)**
Like any muscle, the left ventricle responds with hypertrophy when exposed to increased workload, but the increase in left ventricular thickness is a double-edged sword. LVH is adaptive and compensatory in its early stages, providing the systolic force needed to maintain cardiac output while keeping a normal wall tension [15]. However, this initial adaptive response alters the physical and functional properties of the human ventricle. Biochemical signaling, including the activation of cytosolic and nuclear messengers in response to hypertrophic stimulus to the cardiomyocyte, affects the morphologic alterations associated with LVH by regulating gene expression. The resulting physical alterations include cardiomyocyte longitudinal and cross-sectional growth and an increase in interstitial and perivascular connective tissue [16, 17].

The left ventricular pressure of a normal, non-hypertrophied heart rises to a peak during systole and fall to its nadir during diastole. Because the pulmonary circulation is “exposed” to the left ventricle during diastole, a low pressure at end diastole “protects” the lungs from excess volume and pressure which could impact oxygenation [18]. In HFpEF patients, left ventricular diastolic pressures fail to fall to physiologically normal levels, leading to increased left atrial and pulmonary pressures. The exposure of pulmonary vasculature to elevated pressures leads to pulmonary edema with clinical consequences including progressively reduced exercise tolerance, hypoxia, and in some cases, even death [19].

Numerous recent therapies developed to counter HFpEF have been largely unsuccessful in delivering the robust clinical benefits needed by the rapidly increasing population of patients with HFpEF. The reduction in mortality and morbidity that device-based and pharmacologic therapies have provided to patients with systolic heart failure do not yet exist for HFpEF patients [20] and the lack of suitable animal models have been identified as one of the primary obstacles for therapeutic innovation in HFpEF [21].

**GIRAFFE: A NATURAL ANIMAL MODEL**

**Developmental Physiologic PLVT**
Species-specific cardiovascular adaptations found in *Giraffa camelopardalis*, the modern giraffe, may represent a naturally occurring model of resistance to HFpEF. At birth, the thickness of the giraffe ventricle is comparable to what has been observed in other young mammals [22]. Over the course of development and general somatic growth, the lengthening of the neck increases the vertical distance between the heart and the brain, requiring systolic blood pressures of 2-300 mmHg at heart level to maintain cerebral perfusion. While dangerously hypertensive by non-giraffe mammalian standards, these pressures are normal and crucial for a giraffe's hemodynamics performance [22-28].

As afterload increases with somatic growth, the giraffe’s left ventricle thickens to alleviate increased wall stress as the Law of Laplace would predict. In humans with systemic hypertension, the left ventricle also thickens to maintain normal wall stresses despite increasing afterload (Figure 1). Progressive thickening reduces the relative size of the ventricular cavity [30]. Deposition of interstitial fibrosis leads to increased ventricular stiffness (reduced compliance). Studies of mammalian heart structure reveal highly conserved, patterned relationships between left ventricular...
wall thickness and cavity size. In modern giraffes, this relationship is uniquely altered although a reduced stroke volume consistent with reduced cavity size is present.

**Figure 1.** Comparison of the giraffe ventricular response to developmental PLVT vs. the human ventricular response to chronic hypertension-induced left ventricular thickening. Hypertension-induced left ventricular PLVT in humans leads to heart failure (HFpEF). Developmental PLVT in growing giraffes does not compromise exercise capacity, an important adaptation for a prey species.

As shown in the phylogeny (Figure 2), giraffes and okapi diverged from their shared common ancestor 10-12 million years ago, and it is over this period of time that the iconic long neck of the giraffe evolved [29].
The divergence of the giraffe from the okapi and other mammals. Made using the Interactive Tree of Life [31].

The proposed fitness-enhancing benefits of the long neck include greater access to high foliage, enhanced predator detection, and sexual selection [32]. But, the survival and reproductive benefits of a longer neck also introduced a unique physiological challenge for the adult giraffe cardiovascular system, namely the obstacle of providing adequate cerebral perfusion of a brain situated over two meters above the left ventricle. The adaptations sparked by this hemodynamic challenge are the core of what may be a new approach to HFpEF.

The gross left ventricular morphology of the modern giraffe shares some but not all characteristics found in other mammals [33-35]. For example, the size and mass of the giraffe heart itself are similar to what is found in similarly-sized mammals. However, relative to other species, the volume of blood contained in the giraffe’s left ventricular cavity is notably smaller, especially compared with the thickness of its ventricular wall [26, 27]. The uniquely high ratio between left ventricular wall thickness and cavity size in the adult giraffe is thus a highly notable deviation; a human with a comparable ratio would be highly symptomatic with a poor clinical prognosis.

**Exercise Intolerance vs. Tolerance**

Humans with advanced LVH often experience exercise limitations and the disease symptoms often associate with physical activity. Cellular, structural and functional alterations induced by LVH compromise the ability of the left ventricle to relax during the diastolic phase of the cardiac cycle [36]. This effect is exacerbated in physical activity when heart rates rise and diastolic filling times are shortened. The severe symptoms and functional limitations in patients with advanced HFpEF are often resistant to pharmacologic intervention. The heart failure syndromes associated with hypertension are considered unavoidable consequences of ventricular hypertrophy.
The developmental pressure-induced left ventricular wall thickness increase (PLVT) of the giraffe heart has special relevance for HFpEF because it is an example of a mammalian heart where PLVT does not appear to impact exercise capacity. The hemodynamic consequences of pathological left ventricular PLVT (human heart failure patient) versus developmental PLVT (normal giraffe) are shown in (Figure 3).

**Figure 3.** Comparison of healthy human adult, human heart failure, and healthy adult giraffe hearts in terms of gross ventricular anatomy and left atrial and ventricular pressure relationships. Despite significant PLVH left ventricular thickening giraffe cardiac pressures do not show the elevated left atrial and ventricular pressures seen in humans with severe PLVH. Giraffe ventricular pressures adapted from Smerup et al., 2016 [27].

The absence of exercise intolerance in giraffe points to unique adaptations allowing their hearts to maintain normal wall stress in the face of rising afterload through myocardial wall thickening without compromising diastolic relaxation and exposing pulmonary circulation to increased pressure. Maintaining superb exercise capacity is of clear importance in a prey species like the giraffe who must flee predators who chase them at speeds as high as 60 km/hr [37]. In a particularly impressive study, heart rates up to 170 min\(^{-1}\) were measured by radiotelemetry in freely moving giraffes as they were running to avoid capture. During flight from predators increased myocardial oxygen demand contributes to rising heart rates which reduces relative diastolic filling times. Although hemodynamic measurements of giraffes exercising at maximum capacity are not presently available, the importance of fleeing for a prey species is self-evident [25].

**Simulated Exercise: Emerging Support for Hypothesis**
Recently an unpublished investigation measured left ventricular pressures during a pharmacologically-induced simulation of predator-evasion autonomic physiology. Progressive
infusion of norepinephrine was administered to mimic the heart rates and blood pressures previously measured in fleeing giraffe, a condition associated with high sympathetic tone. This protocol raised heart rates and blood pressures to levels which exceeding Van Critters’ measurements in exercising giraffes [25]. Heart rates rose from 27b/m at rest to 118b/m 3 minutes and 150b/m six minutes into the infusion. Blood pressures rose three-fold from 167mmHg at baseline to over 500mmHg at peak infusion. Of note was the absence of appreciable elevation in left ventricular pressure during diastole despite tachycardia and extremes of afterload. This finding supports the hypothesis that evolved adaptive mechanisms preventing diastolic compromise at extremes of afterload and heart rates protect this prey species from fitness-reducing exercise intolerance seen under similar conditions in humans with PLVT.

**Potential Mechanisms**

The cellular and subcellular mechanisms that protect giraffe hearts from the adverse hemodynamic consequences of PILT remain largely unidentified and characterized. However, unique mutations in the modern giraffe genome point to fibrosis suppression as a possible mechanism. In humans, interstitial fibrosis contributes to ventricular stiffening and subsequent diastolic impairment in HfPEF. While numerous interdependent systems are involved in the deposition of collagen and extracellular matrix proteins in myocardial fibrosis, the renin-angiotensin system (RAS) plays a central role in this cascade [38]. Angiotensin-converting enzyme (ACE), a key enzyme in the RAS, converts decapetide angiotensin I to octapeptide angiotensin II, which has numerous effects on vascular and myocardial tissue. Notably, angiotensin II plays an important role in hypertension-induced fibrosis [39-41].

An observed relative absence of fibrosis in giraffe myocardia (in comparison with similarly thickened human ventricles) may be linked to the unique mutation in the ACE genes of the giraffe genome [25]. A comparison of the giraffe genomes and the genome of its closest living evolutionary relative, the okapi, found 70 genes with “multiple signs of adaptation” not seen in other eutherian mammals [29]; five of these genes are found within the developmental pathways that lead to cardiac fibrosis [42]. Preliminary data from reviewing 136 necropsy reports suggests a reduced propensity for myocardial fibrosis in the giraffe relative to humans and other mammalian species [42].

Because fibrosis impairs ventricular diastolic relaxation in humans, potential fibrosis inhibition mechanisms in the giraffe may underlie its preserved exercise capacity. There are undoubtedly multiple interdependent mechanisms involved in the unique diastolic physiology of these animals. It is currently unclear how differences in autonomic regulation, myocardial innervation, neuroendocrine function and other factors contribute to a giraffe’s unique exercise capacity. Far clearer is what the modern giraffe sprinting on the savannah represents to the field of human heart failure: a high-performance model of preserved exercise capacity in the presence of significant PILVT.
RECOGNIZING EVOLUTIONARY ADAPTATIONS AS A SOURCE OF THERAPEUTIC INNOVATIONS

The giraffe’s unique physiology has long been a source of fascination to biologists and physiologists. Goetz and Keen, two of the first to gather concrete physiological data on the giraffe noting its ‘high’ blood pressures, by human standards. Others have studied the giraffe’s resistance to orthostatic changes with shifts in neck position and the ability of its kidneys to withstand high arterial pressures [23, 43-55]. Earlier studies show thick ventricular walls in the giraffe [23, 27]. Smerup et al. studied the giraffe’s ability to generate and sustain high afterload investigating myocardial architecture, cellular structure and hemodynamics [27]. Their findings included a left ventricular pressure time curve demonstrating normal diastolic ventricular pressures. While the animal was under anesthesia and not tachycardic, normal diastolic pressures would not be predicted in a morphologically comparable ventricle.

The importance of this finding to human cardiovascular medicine is significant. The existence of a mammalian cardiovascular system in which progressive PLVT is not accompanied by reduced diastolic relaxation or elevated cardiopulmonary pressures disrupts conventional paradigms. It directs attention away from pharmacologic therapies directed at altering lusitropic characteristics of myocardial tissue and towards developmental pathways and related regulatory systems.

Within the field of cardiovascular medicine, numerous species exhibit physiologic characteristics with salience for human health. Okapi are uniquely vulnerable to peripartum cardiomyopathy, a heart failure syndrome associated with late pregnancy in women [56]. Some avian taxa, parrots and pigeons, develop significant atherosclerosis in captive settings more than others [57]. Groups of rock kangaroos with increased ventricular thickening have been noted to have elevated sudden death risk suggesting the species may be a natural animal model for hypertrophic cardiomyopathy, the leading cause of cardiovascular death in young human athletes [58]. Many other species exhibit unique sets of cardiovascular physiologies with relevance to a wide range of human disorders. Some

Given the salience of PILT in the giraffe other species-specific cardiovascular characteristics to human health, why are connections relatively unexplored? One factor has been the limited extent to which physicians perceive the natural world as a source of insights for complex human pathophysiology. Amongst veterinarians and wildlife biologists, training in comparative physiology, emphasizing differences between species and seeking to define general principles, is a core discipline that underpins any understanding of how animals interact with their environment. Yet, modern medical education does not traditionally include broad instruction on the diverse range of high-performance physiologies of other species. Greater collaborative interactions between physicians, veterinarians, animal physiologists and wildlife biologists would increase the likelihood that biomedical investigators would identify a ‘solution’ to challenging human pathophysiologies in the natural world.

Rudolf Virchow, father of modern pathology, observed that, “Between human and animal medicine there is no dividing line” [59]. Despite Virchow’s early insight, the separation between human, comparative and veterinary cardiology persist, and the lack of communication between these research fields impede innovations to the detriment of human cardiovascular disease. As physicians and investigators increasingly perceive biodiversity in the natural world as a source of insights for clinical medicine, bioinspired solutions to the most challenging cardiovascular issues may emerge.
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