Heart Failure Canine Research at Wayne State University: Concerns about Scientific Merit and Cruelty to Animals

Physicians Committee for Responsible Medicine
Washington, DC, USA

February 2014

Canine Heart Failure Research at Wayne State University: A Summary

Tens of millions of dollars of research funding are spent on animal models of heart failure every year, but available treatments are quite limited in number and sustained effectiveness. Dr. Donal O'Leary of Wayne State University has received more than $8 million in NIH funding since 2000 and more than $5 million for one completed and one ongoing grant for his canine heart failure research. Yet our analysis shows that he has produced nothing to advance heart failure prevention or management.

The lack of translational success of heart failure animal research is primarily attributable to species differences in cardiovascular physiology and pathophysiology, and to the inability to replicate human heart failure causes, natural history, manifestations, complications, and responses to treatments. Animal models of human heart failure are very limited in their ability to provide a useful understanding of human heart failure or to evaluate potential therapeutic measures with reliable translation to heart failure patients.

In Dr. O'Leary's laboratory, heart failure is induced in dogs by rapid ventricular pacing to increase heart rate from the normal range of 60-160 beats per minute to 225-250 beats per minute for several weeks, using surgically implanted electrodes. Dogs in Dr. O'Leary's heart failure and hypertension experiments undergo multiple sequential surgeries for implantation of various devices (such as pacing electrodes, blood pressure transducers, and blood vessel occluders) in their hearts and in the arteries and veins of the chest, abdomen, neck, and limbs. Wires and cables from these devices exit through the skin and are connected to instruments to measure various parameters of cardiovascular function, including heart rate, blood pressure, cardiac contractility, volume and distribution of blood pumped by the heart, and vascular dynamics. Because of the nature and the number of surgeries, and the number of devices inserted into the dogs, many serious and even lethal complications have occurred during surgeries, recovery periods, and subsequent experiments. One-fourth or more of the research dogs die before completing the testing protocol.

The relevance of experiments in Dr. O'Leary's laboratory to human health, especially regarding translation of his research results to advances for human heart failure, appears to be absent. His experiments have not contributed to the few areas of relative success in heart failure treatment, such as angiotensin converting enzyme inhibitors, beta blockers, bypass surgery, heart transplantation, and mechanical devices. By our analysis, Dr. O'Leary's research has been unreliable, unnecessary, and unproductive. His experimental results often do not correlate with human results, and more reliable results are obtained from similar research involving humans. Citation analysis and literature review evidence also indicate that Dr. O'Leary's research has not advanced human medicine.

According to the Michigan Department of Community Health, Detroit, Wayne County, and Michigan have cardiovascular death rates higher than that for the United States overall. Given the mission of Wayne State University to "improve the overall health of the community," resources should be allocated to research and interventions that provide health returns on investment, such as advances in the understanding, prevention, and treatment of human cardiovascular diseases. We believe that Dr. O'Leary's dog experiments have contributed nothing to this purpose, and should be ended.

1. Introduction

Heart failure is the leading cause of hospitalization in the United States [1]. Heart failure is a major cause of morbidity and mortality, affecting more than five million Americans, directly causing about 60,000 deaths and contributing to more than 200,000 other deaths every year [2,3]. Mortality remains high, greater than 50 percent within five years of diagnosis. Research has provided an understanding of mechanisms underlying various aspects of heart failure, although some molecular and physiological aspects remain unclear. Human-based research has provided a wealth of information on human heart failure. However, many basic science research studies have been devoted to studying heart failure in various animal models ranging from fruit flies to mice to nonhuman primates [4,5].

Tens of millions of dollars of research funding is spent on animal models of heart failure every year, yet this research has not produced effective means of prevention or durable treatments. Even the most widely prescribed drugs do not provide sustained survival advantage and have many adverse side effects. This report will provide evidence that the widely used canine model for heart failure is unreliable and unproductive, as exemplified by the canine experiments conducted by Dr. Donal O'Leary since 2000 at Wayne State University.

2. Background

2.1 Human heart failure

Human heart failure is a complex, heterogeneous disease primarily caused by coronary artery disease, hypertension, and diabetes mellitus. Other common causes include valvular heart disease and myocarditis, and influencing factors include age, gender, ethnicity, family history, and lifestyle issues such as obesity, dietary content, and cardiovascular fitness [6,7]. Few interventions have significantly impacted survival in heart failure, and mortality remains quite high, with most patients deceased within five years after diagnosis.

2.2 Animal models of heart failure

Many different models have been generated using animals in attempts to study various aspects of human heart failure. Animal models may be categorized as small animal models (primarily mouse, rat, rabbit, and cat models), and large animal models (primarily dog, pig, cow, and nonhuman primate models). This report will address dogs as a model for human heart failure, because this is the species used in Dr. Donal O'Leary's experiments at Wayne State University.

Several techniques are widely used to create heart failure in dogs: rapid cardiac pacing, coronary artery microembolization, coronary artery ligation, volume overload, pressure overload, mitral valve avulsion, transmyocardial direct current shock, toxic agents, dysrhythmias, and hypertension [4]. Figure 1 displays the animal models of heart failure used at Wayne State University. This report will focus on the canine chronic heart failure model induced by rapid pacing, as this is the model employed by Dr. O'Leary.

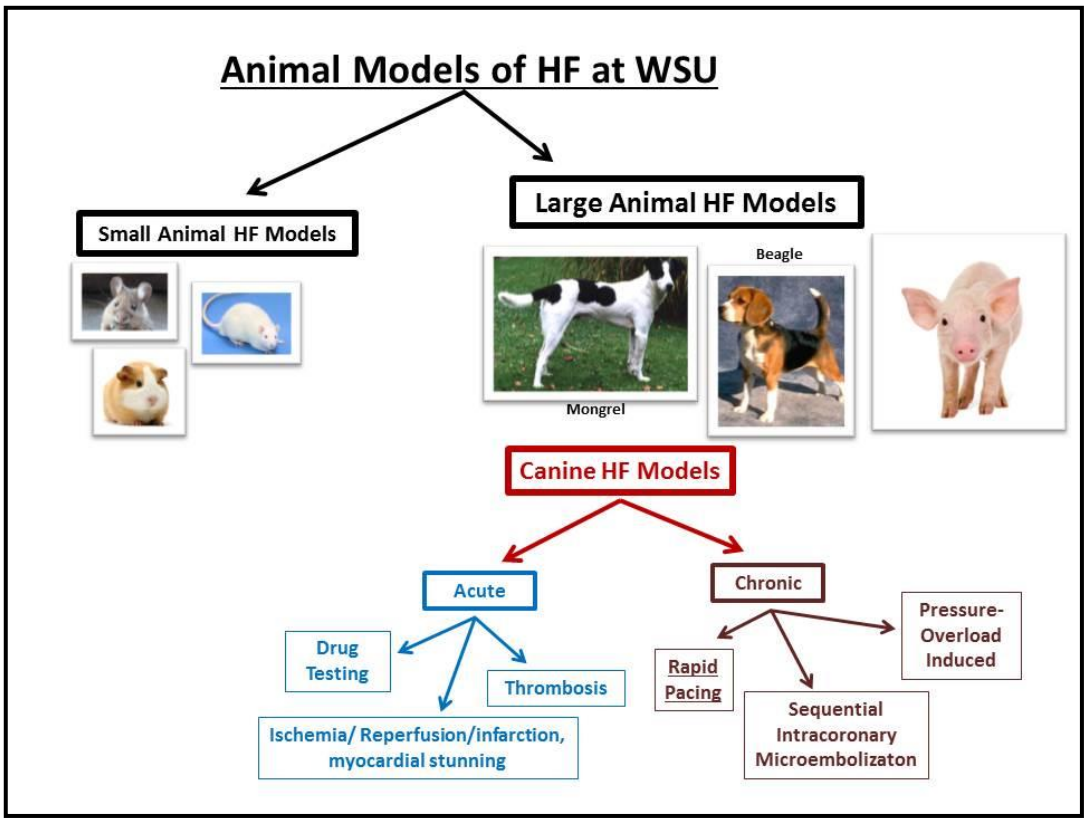

Figure 1: Animal models of heart failure at Wayne State University

3. Experimental protocols

Dr. O'Leary's laboratory investigates the integrative control of the cardiovascular system (neural and hormonal control of heart rate, cardiac output, blood pressure, regional blood flow, and sympathetic nerve activity) under normal and exercise conditions, using dogs who have undergone multiple surgeries for implantation of mechanical and monitoring hardware. Over the past 14 years, Dr. O'Leary has added heart failure and hypertension experiments in order to determine how cardiac pathophysiological changes modulate the integrative control of cardiovascular events during exercise in dogs.

3.1 Acquisition of dogs

Wayne State formerly purchased dogs for Dr. O'Leary's experiments from a Class B random source animal dealer who obtained the dogs from animal shelters and other sources. In 2012, likely due to a series of Animal Welfare Act violations by his Class B supplier, Dr. O'Leary began purchasing purpose-bred dogs from Class A animal dealers. Once the dogs arrive at the research facility, they are given about a week to acclimate to the environment at the animal facility, physical handing by laboratory staff, and exercising on a treadmill. In general, Dr. O'Leary has used healthy adult mongrel and beagle dogs of both sexes and variable weight.

3.2 Surgeries and instrumentation

After the acclimation periods, dogs undergo their first set of surgeries. Following a variable recovery period, they are subject to additional surgeries depending on the experimental requirements. Dogs in Dr. O'Leary's experiments may have up to 4 sequential surgeries (all requiring the use of general anesthesia), with usually 7-10 days of recovery time between surgeries and between the last surgery and initiation of the experiments.

Common procedures used in Dr. O'Leary's laboratory are thoracotomy, sternotomy, left flank abdominal surgery, arterial occlusion, and chronic instrumentation. Either a thoracotomy or median sternotomy is performed in order to insert cardiac and vascular monitoring hardware, depending on dogs' anatomical features [8-10]. Sternotomy is a more complicated and painful surgery that causes more operative trauma and requires more postoperative care and recovery time, compared to a thoracotomy [11].

A catheter is inserted into the heart to measure left ventricular pressure, and a blood flow transducer is placed around the ascending aorta to measure cardiac output. Ventricular pacing electrodes are sutured to the right ventricular free wall. In other procedures, hydraulic vascular occluders are placed on the superior and inferior vena cava. Two pairs of sonomicrometry crystals are placed on the left ventricular surface to measure contractility changes under various conditions. The pericardium is then reapproximated loosely, and the chest is closed in layers [9].

A second set of surgeries is performed, usually 7-10 days later. Through a mid-ventral abdominal approach or left retroperitoneal approach, blood flow transducers are placed on the terminal aorta and/or left renal artery to measure blood flow to the hindlimbs and left kidney, respectively [8,12]. Distal to the flow probe, a vascular occluder is also placed on the terminal aorta to facilitate gradual vascular occlusion. All arteries branching from the aorta between iliac arteries and the hindlimb flow probe are ligated and severed, and a catheter is placed through a lumbar artery to measure systemic arterial pressure [9]. For hypertension studies, partial unilateral renal artery occlusion is performed to induce hypertension [12].

In some studies that require forelimb blood flow measurements, a third surgery is performed through an axillary incision to insert a blood flow transducer on the right axillary artery that supplies oxygenated blood flow to the forelimbs. In another procedure, arterial and venous catheters are implanted into small side branches of the femoral artery and vein to measure femoral arterial pressure and to infuse drugs, respectively. To monitor central venous pressure, an additional catheter is inserted into a jugular vein and advanced to the atriocaval junction [13].

At the end of each surgical procedure, wires and cables from the implanted hardware are channeled subcutaneously and exteriorized between the scapulae [13], to be connected to data recorders. These dogs retain the implanted hardware and the exteriorized wires and cables until they die either postoperatively, during the experimental protocol, or by euthanasia when experiments are completed. Due to the number and nature of the surgeries, and the number of devices implanted, serious or lethal complications are not uncommon. Dr. O'Leary's laboratory has a 25-30 percent death rate for dogs during surgery, recovery, and the experiments, before experimental protocols are completed.

3.3 Induction of heart failure

In Dr. O'Leary's experiments, heart failure is induced by rapid ventricular pacing, using the surgically implanted right ventricular pacing electrodes. The duration of pacing varies depending on the severity of heart failure needed for a particular protocol. For most experimental purposes, dogs' hearts are paced at 225-250 beats per minute (compared to normal 60-160 beats per minute) for about 30 days [14]. Once heart failure is established, exercise experiments are performed to obtain data under heart failure conditions. The pacemakers are disconnected 15-30 minutes before data acquisition [9,10,14]. Researchers have reported various signs of canine heart failure such as extremity edema, ascites, anorexia, and lethargy in rapid ventricular pacing animal models [15].

3.4 Data acquisition

In general, experimental data acquisition is performed before and after surgeries and instrumentation, so each dog can serve as his or her own control animal. For a typical experimental design, the initial set of data is acquired at rest for normalization, and then additional sets are acquired at selected workloads ranging from mild to moderate to severe exercise on a motor-driven treadmill. In Dr. O'Leary's laboratory, mild exercise is typically defined as 3.2 km per hour with 0% elevation, moderate exercise is 6.4 km per hour with 10% elevation, and severe exercise is 8 km per hour with 15-20% elevation [16,17]. Sometimes two experiments are performed on the same day with about 30 minutes between the experiments [13]. Several parameters of cardiac performance (such as heart rate, cardiac output, stroke volume, rate of rise of left ventricular pressure [dP/dt)], and mean arterial pressure) are measured using the surgically implanted devices connected to data acquisition systems through the exteriorized wires and cables. Additional experiments on the treadmill are conducted after heart failure is induced, for comparison of measured parameters obtained with and without heart failure. It has been reported that under heart failure conditions, only some animals are willing to exercise beyond the mild workload [10].

4. Experimental findings

The primary aim of Dr. O'Leary's experiments since 2000 has been to study the interactions between active skeletal muscle and the cardiovascular system during dynamic exercise in the absence and presence of heart failure and hypertension. During exercise, oxygen delivery to skeletal muscle must increase to meet the increased metabolic demand of working muscle. Various metabolites (such as lactic acid, arachidonic acid, adenosine, hydrogen ions, and potassium ions) are formed by biochemical pathways in working skeletal muscle, and in turn activate physiological responses in order to increase blood flow and oxygen delivery to exercising muscle. In a process termed the *muscle metaboreflex* (MMR), these metabolites prompt chemically sensitive nerves located in muscle to evoke an increase in sympathetic nerve activity. This leads to systemic cardiovascular responses, primarily the control of heart rate, cardiac output, blood pressure, and muscle blood flow distribution.

Experiments conducted in Dr. O'Leary's laboratory from 1992-2002 were designed to study MMR-mediated control of the cardiovascular system, and the mechanisms underlying these systemic circulatory responses, during mild to severe exercise in dogs. Several publications from this era showed that MMR during dynamic exercise increased heart rate [18,19], cardiac output [20], cardiac

contractility [21,22], and right atrial pressure [23], and also evoked a systemic vascular pressor response [24], including in active skeletal muscle [13,25]. However, increases in cardiac contractility were limited by coronary vasoconstriction [26]. It was further shown that exercise activates parasympathetic activity in addition to sympathetic activation [27], and that MMR improves oxygen delivery to active skeletal muscle [28].

From year 2000 to present, Dr. O'Leary has induced heart failure and hypertension in dogs to determine what happens to MMR-mediated cardiovascular responses under pathological conditions, repeating his previous experiments to compare dogs without and with heart failure. The first heart failure study showed that the strength and mechanisms of the MMR are altered under heart failure conditions — cardiac output does not increase, and the systemic arterial pressure increases only by peripheral vasoconstriction [8]. This was confirmed four years later when the effects of arterial baroreflex pressor response were observed to have different strengths and mechanisms during heart failure [29].

Over the next few years, Dr. O'Leary conducted studies in which various parameters of the MMR were studied in dogs with heart failure. It was shown that under heart failure conditions MMR-mediated ventricular function is impaired [30], coronary blood flow and ventricular function are altered [31], arterial baroreflex is altered [32], MMR-mediated increase in ventricular contractility is abolished [17], baroreflex control of heart rate is impaired and altered [10,33,34], and dynamic control of maximal ventricular elastance is abolished [35]. Dynamic exercise and MMA reduce baroreflex control of heart rate and cardiac output, and these control functions are substantially impaired in dogs with heart failure [9,14]. A more recent canine model of hypertension has shown that exercise intolerance seen with hypertension may be due to impaired ability of MMR to mediate increased cardiac function [12]. Dr. O'Leary has also investigated cardiovascular responses and MMR during recovery from pacing-induced heart failure [36].

5. Analysis of Dr. O'Leary's canine experiments: limitations and human relevance

Critical analysis of the studies conducted in Dr. O'Leary's laboratory identifies many limitations that can be broadly categorized as technical (or methodological) limitations or limitations regarding translation and applicability for humans.

5.1 Technical limitations

There are numerous technical issues that complicate data acquisition and interpretation, and thus contribute to failure to replicate findings in human heart failure. A few examples are discussed here to illustrate this point. In some studies, monitoring devices display conflicting findings when the same parameter is measured with two different techniques. For example, the cardiac stroke volume calculated from the sonomicrometry crystals placed on the heart regularly underestimate (by as much as 54%) the stroke volume obtained with an ultrasonic probe placed on the ascending aorta [22].

Arterial baroreflex is the body's natural mechanism to maintain blood pressure within a normal range. In the majority of experiments conducted in Dr. O'Leary's laboratory, the arterial baroreflex in the dogs is intact and functional. Therefore, changes in blood pressure accompanying MMR activation are also affected by the baroreflex, which opposes MMR-mediated pressor changes. It was shown that arterial

baroreflex alters the strength and mechanisms of MMR by decreasing the MMR-mediated pressor response through inhibition of MMR-mediated peripheral vasoconstriction [37]. Thus, data regarding MMR-mediated changes, an essential component of many of Dr. O'Leary's experiments, are compromised because the counterbalancing regulatory effects of innate arterial baroreflex activation cannot be segregated.

Furthermore, by the use of only spontaneous blood pressure and heart rate changes, the analysis is "inadequate to evaluate the full stimulus-response curve of the arterial baroreflex (i.e., threshold, saturation, and linear operational range of the reflex)" [10]. This further limits data interpretation, as decreased baroreceptor sensitivity seen in heart failure that "may have resulted from a shift to a nonlinear region of the baroreflex stimulus-response relationship cannot be discounted" [10]. Another limitation of this technique is that only the changes in heart rate in response to rapid, transient changes in arterial blood pressure can be measured. These changes are, however, due mainly to parasympathetic mechanisms and do not allow the researcher to investigate the sympathetic component of the baroreflex. In confirmation, Dr. O'Leary has written that his observations are "confined to the parasympathetic component of baroreflex…and it is unknown whether and how heart failure affects the sympathetic component" [10]. In addition, cardiac anatomic and functional changes caused by rapid pacing can interfere with experimental findings. Dr. O'Leary's laboratory stops pacing only 15-30 min before acquiring experimental data [9,10,14]. Other canine heart failure researchers often reduce pacing to 190 beats per minute for 2-3 days once heart failure is established, to stabilize the condition [15,38]. Since cardiac output is the product of stroke volume and heart rate, any variability in heart rate or cardiac function will directly affect cardiac output.

It is possible that arterial occlusion in dogs generates a sympathetic response not solely due to MMR. The carotid sinus baroreceptor reflex can lead to spleen contractions in dogs, and the spleen can act as a venous reservoir to mediate blood volume shifts in the systemic vascular beds in dogs [39-41]. These effects cannot be prevented unless dogs are splenectomized, nor can they be separated from the overall endpoint measurements obtained by the instruments implanted in these dogs. In addition, Dr. O'Leary routinely measures responses originating from the hindlimbs. However, under heart failure conditions where systemic blood flow to all active muscles is reduced, "responses may depend on the relative level of ischemia as well as which muscles are ischemic" [22]. Studies in cats have shown that cardiovascular responses to muscle contraction may differ between the limbs, with forelimbs evoking a greater response than hindlimbs [42]. Taken together, these limitations significantly influence data acquisition and interpretation.

Heart failure is typically accompanied by biochemical and structural changes in the heart, from DNA expression levels in cardiac myocytes to organ function. Markers of biochemical and structural changes are routinely utilized to diagnose and treat heart failure in humans [43]. While Dr. O'Leary's experiments report basic functional data (heart rate, cardiac output, stroke volume, rate of increase of pressure, and other measures), they have not consistently reported corresponding biochemical changes that accompany pacing-induced heart failure in dogs. Though these data would not improve translation or application for humans, their absence makes it difficult even to determine whether dogs develop comparable and reproducible pathologies from study to study.

5.2 Human relevance: muscle metaboreflex studies

The primary problem of Dr. O'Leary's canine MMR experiments is the lack of relevance to human disease states. Dr. O'Leary's publications have characteristically aimed to extrapolate canine data to humans as if there are no species differences, despite contradictory evidence from human studies. Michael J. Joyner, who has performed similar studies in humans, states of Dr. O'Leary that "he deftly (using selective interpretation) dismisses the human data as either irrelevant or incomplete" [44]. Loring B. Rowell, in critiquing the use of dogs and other animals to study human cardiovascular responses [45], states: "No amount of extrapolation would have revealed particular features of human physiology that set this species apart." Rowell further states: "Nor can the overall problem of coping with the stress of prolonged exercise in humans be appreciated from studies with these laboratory animals."

For example, Dr. O'Leary has reported that MMR restores blood flow to contracting muscles during exercise in dogs [46]. In contrast, Joyner et al demonstrated that the pressor response to ischemic exercise does not improve blood flow to contracting muscles in humans [47]. Rather, MMR produces a marked increase in muscle sympathetic nerve activity that leads to vasoconstriction, which in turn limits the ability of the rise in pressure to improve blood flow to the contracting muscles.

MMR-mediated cardiovascular responses during exercise have been studied in humans under numerous conditions: high altitude [48]; in-flight on a space shuttle [49,50]; after exposure to simulated microgravity [51]; under conditions of hypoxia [52], dehydration [53], and exposure to humid heat [54], and after water ingestion [55]. MMR has also been studied comparatively for sprinters and distance runners [56], for pre-adolescent boys and adult men of various ages [57,58], and for graded intensities of MMR activation [59]. The abundance of information regarding the effects of MMR and other elements of exercise and heart failure in humans appears to make Dr. O'Leary's less relevant experiments using dogs unnecessary.

5.3 Human relevance: Comparative canine and human anatomy and physiology

Different anatomical and functional adaptations between bipedal and quadrupedal species have resulted in different physiological responses in humans and dogs. In humans, there is a greater blood pressure gradient between heart, head, and feet, and redistribution of blood flow is an important physiological response that enables our species to deal with changes in posture, exercise, and heat exposure [45]. Blood flow distribution varies importantly between humans and dogs, both at rest and during exercise. Blood volume redistribution during exercise is very small in healthy dogs [45,60].

In upright humans, about 70 percent of total blood volume is below heart level, and 70 percent of this is in compliant veins. In upright dogs, about 70 percent of blood volume is at or above heart level. Central blood volume, central venous pressure, and stroke volume are relatively low in dogs under resting conditions. Exercise increases stroke volume by about 40% in upright humans. In contrast, dogs increase stroke volume relatively little, since it is close to maximum due to pericardial constraint [45,61]. Exercise results in redistribution of visceral blood flow in humans, whereas this does not occur in dogs [61]. As mentioned previously, spleen contractions that occur during exercise in dogs have an important effect on systemic blood volume redistribution, but this does not occur in humans [39,40].

The size of the heart relative to body weight is three times greater in dogs compared to humans, and cardiac pumping capacity per kilogram of body weight of dogs exceeds that of humans by two to three times [45,61,62]. There are also “quantitative differences that become important when data are compared among species that dramatically differ in heart size” [63]. Maximal oxygen consumption ($VO_{2\ max}$) is more than three times higher for exercising beagles than for exercising humans, and also varies severalfold even among dog breeds. Had Dr. O’Leary used racing dogs or sled dogs for his experiments, the cardiovascular responses would have been very different.

5.4 Human relevance: pacing-induced heart failure

Pacing-induced heart failure in dogs produces cardiac dysfunction that is etiologically and temporally unrelated to human heart failure. Human heart failure is a complex multifactorial disease significantly influenced by genetic, environmental, and lifestyle factors. A large majority of heart failure prevalence in humans is due to coronary artery disease, hypertension, and diabetes. The differences between the etiology, natural history, mechanisms, progression, and complications of heart failure in humans and experimentally induced heart failure in dogs complicate translation of results from dogs to humans. In fact, the pathogenesis of heart failure in rapid-pacing canine models is not completely understood.

Important differences between human heart failure and pacing-induced canine heart failure exist. For example, circulating levels of atrial natriuretic peptide and brain natriuretic peptide are known to be increased in human heart failure [64] and are differentially regulated during exercise in heart failure patients [65]. In contrast, plasma atrial natriuretic peptide level is diminished in pacing-induced heart failure in dogs [66]. Other molecular studies have shown that, unlike human heart failure, rapid pacing-induced functional changes in the canine heart are not associated with increased left ventricular mass [4]. Rapid pacing using a protocol similar to that used in Dr. O’Leary’s laboratory has shown that within 4 weeks, cardiac dysfunction can occur from a marked decrease in cardiac myocytes from programmed cell death known as apoptosis [38].

Cardiac muscle stiffness seen in both human heart failure and canine rapid-pacing heart failure is due in part to the changes in expression levels of structural proteins in the myocardium. However, expression patterns of even the same structural proteins in humans and dogs are different. For example, the expression of the structural protein titin decreases significantly in human heart failure [67], while there is no change in total titin amount in canine heart failure [68]. Furthermore, in contrast to human heart failure, rapid pacing decreases the content and structure of collagen in canine hearts [4]. Thus, the *loss* of collagen support contributes to ventricular remodeling in the canine rapid-pacing model, whereas *accumulation* of collagen contributes to myocardial remodeling in human heart failure [69].

At the molecular level, certain cardiac signaling pathways (such as the pathway that mediates the fight-or-flight response) are altered differently in dogs [15]. In addition, epigenetic regulation plays a crucial role in the development of human heart failure, where dysregulation of chromosomal modification (such as histone acetylation) is directly linked to impaired function of contractile cells of the heart [70]. These processes are very different among animal species [71].

Rapid-onset development of pacing-induced heart failure in dogs does not resemble the slow, progressive development of heart failure in humans, which is typically the end stage of

pathophysiological alterations following myocardial infarction, hypertension, diabetes, or infection. The incidence of tachycardia-induced heart failure is low in humans, and it occurs primarily among patients with atrial fibrillation [72] rather than sustained ventricular tachycardia as used in Dr. O'Leary's experiments. Furthermore, canine pacing-induced left ventricular pathophysiology and dysfunction are more reversible than human heart failure, a difference that Dr. O'Leary has investigated in dogs by assessing cardiovascular responses to exercise and MMR during recovery from pacing-induced heart failure [36].

From molecular to organ to whole-animal level, data from the canine rapid-pacing heart failure model do not reliably replicate human heart failure pathophysiology. Balke and Shorofsky stated the complexity of heart failure animal modeling succinctly: "The characteristics of cardiac hypertrophy and heart failure are model-dependent. Even in the same species, the experimental results are profoundly influenced by the method used to create hypertrophy and/or heart failure (e.g., volume-overload, pressure-overload, genetically altered, rapidly paced, coronary artery ligation, etc.)" [73].

5.5 Human relevance: health benefits for Detroit, Wayne County, and Michigan

Our citation analysis of Dr. O'Leary's publications and review of current approaches to prevention and treatment of human heart failure do not identify any contribution from Dr. O'Leary's experiments on dogs. This appears to be inconsistent with Wayne State University School of Medicine's mission statement, which includes a pledge "to improve the overall health of the community." [74]

According to the Michigan Department of Community Health, Michigan has a higher cardiovascular death rate than the United States overall (8th worst among states), loses about 30,000 of its citizens to cardiovascular disease annually, saw more than 60,000 women die of heart disease between 2005-2010 (enough to fill Ford Field for a Detroit Lions football game), and has an annual economic burden of nearly $17 billion (2010 figures) due to cardiovascular disease.

Wayne County has the highest heart disease death rate in Southeastern Michigan, and the City of Detroit heart disease death rate exceeds the statewide rate by 25 percent and the nationwide rate by 40 percent. Wayne County also has the highest heart failure age-adjusted prevalence in Michigan, highlighting the tragedy of wasting funds and time on unproductive experiments. [75-78]

Conclusions

Dr. Donal O'Leary has for 25 years conducted experiments addressing the effects of neuroregulatory and metabolic responses in dogs under various conditions. Since 2000, he has studied the effects of MMR in canine heart failure and hypertension, using instrumented dogs performing treadmill exercise. In our view, analysis of his experimental results provides convincing evidence that these experimental studies have been unproductive for three primary reasons: (1) They are *unreliable* because they are unable to replicate important elements of human heart failure and are often discordant with similar investigations in humans with and without heart failure; (2) They are *unnecessary* because they address experimental hypotheses that are already tested, or could be tested, in human studies, and; (3) They are *clinically unimportant* because they have contributed nothing directly influencing prevention or treatment of human heart failure.

The major scientific barriers in Dr. O'Leary's experiments include technical limitations, anatomical and physiological species differences, and inability to replicate the causes, pathophysiology, and natural history of human heart failure and hypertension. These barriers are largely immutable when dogs are used to study human cardiovascular function and disease, but they have been overcome with the abundance of information from similar studies in humans.

The cruelty of these experiments is self-evident, since dogs undergo as many as four major surgeries resulting in the implantation and exteriorization of as many as 12 devices. They are then made to exercise repeatedly, despite the pain and psychological burden of the instrumentation and sometimes forced exercise. One-fourth or more of the dogs die from the surgery, the postoperative recovery, and complications related to the inserted hardware, before experiments are completed. Those who survive are killed at the end of the experiments.

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