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

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Canine Heart Failure Models at Wayne State University: A Summary

- Tens of millions of dollars of research funding are spent on animal models of heart failure every year. Wayne State University researcher Donal O'Leary, Ph.D., has received more than $8 million in National Institutes of Health (NIH) funding since 2000 for cardiovascular research using animals, more than $5 million of which funded two canine studies addressing heart failure. Yet, in our judgment, this experimentation has produced nothing to advance heart failure management in patients.

- The very limited translational success of animal-based heart failure research is attributable to the extensive species differences in cardiovascular physiology and pathophysiology, as well as to the inability to replicate human heart failure natural history, manifestations, complications, recovery, and responses to treatments in animals. Animal models of human heart failure are extremely 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 at Wayne State, heart failure is induced in dogs by rapid ventricular pacing, increasing heart rate from the normal range of 70-120 beats per minute to 225-250 beats per minute for several weeks, using surgically implanted electrodes.

- In Dr. O'Leary's heart failure and hypertension experiments, dogs undergo multiple sequential surgeries for implantation of various devices (e.g., pacing electrodes, blood pressure transducers, and blood vessel occluders) in their hearts, arteries, and limbs. Wires and cables from these devices protrude through the skin and are connected to instruments in the laboratory to measure various parameters of cardiovascular function (e.g., heart rate, blood pressure, cardiac contractility, and volume of blood pumped by the heart).

- Because of the nature and the number of surgeries and the number of devices inserted into the dogs many severe and even lethal complications have occurred during surgeries and the recovery periods. Twenty-five percent of all of the dogs used in Dr. O'Leary's hypertension/heart failure experiment will be killed due to problems associated with the experimental procedures.

- The relevance of these experiments to human heart failure appears to be limited or nonexistent. Dr. O'Leary's publications have not contributed to the few areas of relative success in heart failure treatment, such as angiotensin converting enzyme inhibitors, beta-blockers, coronary bypass surgery, heart transplantation, and mechanical devices, in our judgment.

- We posit that Dr. O'Leary's research has been unnecessary and wasteful, because the experimental questions and hypotheses he has pursued have been, or could have been, tested and answered in humans with greater accuracy and applicability. Nearly a century of heart failure research involving humans has made animal protocols such as those of Dr. O'Leary superfluous.

- In his scientific publications, Dr. O'Leary appears to extrapolate data from dogs as if they apply directly to humans. A prominent researcher in the same field has criticized Dr.

O’Leary's research by writing that “he deftly (using selective interpretation) dismisses the human data as either irrelevant or incomplete.”

- According to a 2010 Michigan Department of Community Health report, Michigan has a death rate due to cardiovascular disease that is higher than that for the United States overall. Given the obligation of Wayne State University to "improve the overall health of the community," funds would be better spent on cardiovascular research that will provide the greatest health return 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 5 million Americans, directly causing about 60,000 deaths and contributing to more than 200,000 other deaths every year [2, 3].

Research has provided an understanding of mechanisms underlying various aspects of heart failure, but many molecular and physiological aspects remain unclear. Human-based research has provided a wealth of information on human heart failure. However, many experiments have been devoted to studying heart failure in animals 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, and yet these expenditures have not led to a cure for humans; even the most widely prescribed drugs are not curative and have adverse side effects. This appears to be primarily due to the extensive species differences in cardiovascular physiology and pathophysiology. In other words, animal models are unable to replicate the causes, natural history, manifestations, complications, and responses to therapies of human heart failure. Thus, in our judgment, animal experimentation approaches are unable to provide an adequate understanding of human heart failure, reliable replication of human disease processes, or means for evaluating potential therapeutic strategies.

2. Background

2.1. Human Heart Failure

Human heart failure is a heterogeneous disease primarily stemming from coronary artery disease, hypertension, and diabetes mellitus. Other common causes include valvular heart disease and myocarditis, and influencing factors include advancing age, male gender, ethnicity, family history, and lifestyle issues such as obesity and dietary content. Few interventions have been found to substantially prolong survival in heart failure, and no cure is in sight despite decades of experiments using animals.

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. Species used in these models include mice, rats, rabbits, cats, dogs, pigs, cows, and nonhuman primates. Several different techniques are used to create heart failure in dogs. The method currently used in Dr. O’Leary’s experiments at Wayne State is rapid cardiac pacing.

3. Dr. Donal O’Leary’s Canine Experiments

3.1. Experimental Protocols

Dr. O’Leary's laboratory investigates neural and hormonal control of heart rate, cardiac output, blood pressure, regional blood flow, and sympathetic nerve activity under normal and stress conditions induced by treadmill exercise, using dogs who have undergone multiple surgeries for implantation of monitoring hardware. Over the past decade, Dr. O’Leary's laboratory has added heart failure into this equation in order to investigate how cardiovascular function changes during exercise.

Experimental and veterinary records, as well as experimental protocols and publications, were acquired by the Physicians Committee from public sources and through public records requests, and these were reviewed to determine what happens to the dogs in Dr. O'Leary's experiments. This document and all of its statements summarizing Dr. O'Leary's experiments at Wayne State are based on those records, protocols, and publications.

Dogs in these experiments are subjected to as many as four surgeries over a period of six to eight weeks, followed by weeks to months of exercising on a treadmill.

The records of the dogs Freddie and Wilma, obtained from Wayne State, show that they were unwilling to exercise on the treadmill, resulting in them being used for practice surgeries or other procedures, where they were killed with little or no data being collected.

General Statistics on Dr. O'Leary's Canine Experiments

- Total NIH funding provided to Dr. O'Leary since 2000: **$8,483,721**
- NIH funding for two canine heart failure research protocols since 2001: **$5,491,948**
- Death rate of dogs resulting from surgeries and complications in Dr. O'Leary's hypertension experiment: **25 percent**
- Duration of research: **More than 25 years**
- Scientific publications for Dr. O'Leary's dog experiments since 1985: **More than 50**

As illustrated by the veterinary records of the dogs Rogue and Hazel, the first surgery involves making a large incision between ribs and into the chest to expose the heart. Probes are then placed around the aorta and a coronary artery to measure blood flow. Another probe is stabbed directly into the heart to measure blood pressure.

A second major surgery usually follows about two weeks after the first. In this surgery, the abdomen is cut open. Up to six different probes are inserted into or around the major blood vessels. Some probes are hydraulic occluders, used to block blood flow to the kidneys or the legs, which, according to documents obtained by the Physicians Committee, are prone to getting stuck in the occluded (closed) position or rupturing, spilling the occluder fluid into the abdomen.

Depending on the experiment, two more surgeries may be done on the dogs to implant additional probes in other vessels in the neck and legs. Because the probes are solid objects against the fragile internal blood vessels, over time these probes may cause strictures or erosions in the blood vessels, as illustrated by the hole worn through Rogue's aorta, causing her to slowly bleed to death.

The case of the dog Queenie demonstrates other complications that can occur during these experiments. Experimenters accidentally cracked one of the devices implanted in Queenie's body. After fixing the device was attempted, it broke again, retracting into Queenie's body. She was then killed before the experiments were completed.

Each of these probes has to connect to monitoring equipment, requiring that a wire or tube be pulled out of the chest and through the skin. For dogs who have undergone four surgeries, there can be as many as 12 different exit sites. Every place the wire or tube exits the skin is a source of constant irritation, which the dogs try to bite or scratch off, but cannot, due to the jackets and head cones that they must wear. In the case of Rogue, she tried to remove the head cone and jacket many times to relieve the irritation caused by the wires. The exit sites commonly become infected. Over the three months after her chest surgery, Rogue's incisions were repeatedly infected resulting in ongoing antibiotic administration.

Following a one to two week recovery from the final surgery, the experimental procedures begin. The laboratory personnel gradually occlude the dogs' blood flow to their kidneys and/or the lower half of their bodies. This causes hypertension, which exacerbates the hardships of heart failure and multiple surgeries, but the dogs must still exercise on the treadmill. In the heart failure experiments, heart failure is induced by rapid ventricular pacing using implanted electrodes. Dogs' hearts are paced at 225-250 beats/minute (compared to the normal 70-120 beats/minute) for about four weeks to produce heart failure. Once heart failure is established, additional treadmill exercise experiments are performed.

According to Dr. O'Leary, one quarter of all of the dogs used in his hypertension/heart failure experiment were expected to be killed due to problems associated with the experimental procedures. The 2008 version of the protocol titled "Integrative Cardiovascular Control During Exercise in Hypertension"—acquired by the Physicians Committee from Wayne State through the Michigan Freedom of Information Act (FOIA)—states: "We anticipate 25% instrumentation-barodenervation failure within the months of study that requires the animal to be withdrawn from a study and be euthanized." Additionally, in a 2013 Wayne State University Institutional Animal Care and Use Committee Amendment Request Form—acquired through FOIA—associated with Dr. O'Leary's hypertension/heart failure experiment, it is stated: "For our studies, there are situations where instrumentation fails prior to the induction of hypertension or occasionally a dog will no longer run on the treadmill for unknown reasons. When this occurs, those animals are sacrificed…"

Protocols and veterinary records document that every dog used for Dr. O'Leary's heart failure experiments dies, either from the surgeries, during the experiments (as when Rogue bled to death and Queenie's hardware broke and retracted into her body), when the probes or monitors become nonfunctional, or at the end of the experimental protocol.

4. Critical Analysis of Dr. O'Leary's Canine Experiments and Findings

Critical analysis of the studies conducted in Dr. O'Leary's laboratory has identified many limitations that can be broadly categorized as technical (or methodological) limitations or limitations regarding human applicability (due to species-specific regulation of cardiovascular function). An abbreviated discussion of the latter category will follow. Complete analysis and additional references are available from the Physicians Committee.

The primary practical and medically relevant limitation of Dr. O'Leary's research is that in more than 25 years, he appears from our analysis to have not contributed in any direct or meaningful way to the actual benefit of human heart failure patients. Dr. O'Leary has attempted to directly correlate his experimental findings to humans, despite contradictory evidence from human studies. Other researchers in the field of heart failure have been critical of Dr. O'Leary's methods and conclusions, while pointing out that findings from human-based research have been quite different [6-9].

The overarching aim of Dr. O'Leary's laboratory is to study the interactions between biochemical signals produced by active skeletal muscle (muscle metaboreflex) and the resulting cardiovascular responses during dynamic exercise, which involves the continuous movement of muscles and joints. While Dr. O'Leary has described the blood flow-restoring effect of the muscle metaboreflex in his canine experiments, human-relevant studies have shown the opposite effect (decreased blood flow to active muscle) [6-9].

By producing heart failure in dogs by rapid cardiac pacing, Dr. O'Leary created a disease model that is unlike human heart failure, which results from heart attacks, chronic coronary artery disease, hypertension, diabetes mellitus, infections, and other causes unrelated to sustained fast heart rates. In fact, the manner by which heart failure develops in ventricular pacing models still remains unclear. Moreover, rapid-pacing heart failure is reversible [10] in contrast to human heart failure. Therefore, it is not possible to elucidate the molecular mechanisms responsible for human heart failure by studying this rapid pacing model.

Dr. O'Leary has attempted to draw physiological and metabolic conclusions from animals who are anatomically and physiologically unsuitable for comparison to humans. Humans and dogs have very different blood flow distribution patterns related to their obvious anatomical differences. In humans, being vertical, there are much greater blood pressure differences from the heart to the head or the feet, compared with dogs [9].

Redistribution of blood flow throughout the body due to changes in posture or exercise is a critical physiological response for humans [9], but redistribution in healthy dogs is minimal in comparison [9, 11]. About 70 percent of blood volume in a standing human is below the heart, whereas the same percentage is above or at heart level in standing dogs [9]. Humans increase cardiac output during exercise by increasing stroke volume (amount of blood ejected with each heartbeat) by about 40 percent, as well as by increasing heart rate. Dogs are unable to increase stroke volume significantly and thus increase cardiac output by greater increases in heart rate than occur in humans [9, 12].

Humans also accommodate exercise by redirecting visceral blood flow to the central circulation and exercising muscles, whereas this does not occur in dogs [12]. In addition, carotid sinus baroreceptor reflex (the innate blood pressure regulation system) can lead to spleen contractions in dogs, which affects blood volume shifts in the vascular system in dogs [13-15]. Such spleen contractions do not occur in humans. In addition, the size of the heart with respect to body weight is three times larger in dogs compared to humans, and the weight-adjusted pumping capacity of dogs' hearts exceeds that of humans by two to three times [9, 12, 16]. Given these and other physiological differences, it is clear that dogs cannot effectively model the human cardiovascular system.

Many researchers in the United States and around the world have studied the complex interactions among blood pressure, nervous system, skeletal muscle blood blow, and cardiac function in humans undergoing static and dynamic exercise, including heart failure and hypertension patients. In our view, there is no need to study these topics in dogs because doing so at best would produce redundant results and may produce erroneous and nontranslatable results.

Dr. O'Leary's findings regarding the effects of the muscle metaboreflex, a key element in many of his studies, appear to be contrary to findings in humans, who have been studied under various environmental and lifestyle conditions, including: high altitude [6]; in-flight on a space shuttle [17, 18]; after exposure to simulated microgravity [19]; under hypoxic conditions [20]; dehydration [21]; humid heat [22]; water ingestion [23]; under mildly hyperthermic conditions in sprinters and distance runners [24]; in pre-adolescent boys versus men [25] and younger men versus older men [26]; influence of graded intensities of muscle metaboreflex activation [27]; and how aspirin augments baroreflex sensitivity and muscle metaboreflex activation [28].

Since 2000, Dr. O'Leary has tested several hypotheses related to muscle metaboreflex, exercise, and their impact on cardiovascular function under heart failure conditions using rapidly

paced heart failure dogs [10, 29-41]. Dr. O'Leary's findings regarding the cardiac parasympathetic response during exercise, the role of the arterial baroreflex response, the effects of sustained rapid ventricular pacing and artificially induced hypertension, the effects of drugs, and the effects of heart failure on numerous physiological parameters have been studied and, in important instances, contradicted by human observations [42-59].

Other researchers in this field have also commented on Dr. O'Leary's dog experiments and their findings. Loring Rowell, Ph.D., Professor Emeritus of Physiology and Biophysics at the University of Washington School of Medicine has commented on dog experiments that "[no] amount of extrapolation would have revealed particular features of human physiology that set this species apart… Nor can the overall problem of coping with the stress of prolonged exercise in humans be appreciated from studies with these laboratory animals" [9]. Michael Joyner, M.D., a cardiovascular researcher from the Mayo Clinic, wrote of Dr. O'Leary that "he deftly (using selective interpretation) dismisses the human data as either irrelevant or incomplete" [8].

A detailed, referenced, and illustrated discussion of human-based research methods that provide human-relevant findings and conclusions is available from the Physicians Committee.

5. Conclusions

For decades the laboratory of Donal O'Leary, Ph.D., has been investigating cardiovascular responses to dynamic exercise using conscious, chronically instrumented dogs with and without experimental heart failure. In our judgment, his results are not directly applicable to humans, due to technical limitations and biological differences between dog and human cardiovascular physiology and pathophysiology.

Additionally, it appears that Dr. O'Leary's experiments have not contributed to any advances in the management of heart failure patients and has been either wrong or redundant regarding human heart failure. There is a large body of evidence, reported in numerous studies conducted in humans since 1917, showing that it is indeed possible and productive to study these exercise-mediated cardiovascular responses in humans under many different conditions, rather than in instrumented dogs in the laboratory environment. Therefore, cardiovascular studies in Dr. O'Leary's laboratory (and any other Wayne State University laboratories using canine models) should be discontinued immediately. NIH and university funding could be profitably redirected to human-relevant research that builds on the substantial body of information provided from previous and current human-based investigations.

According to the Michigan Department of Community Health, Michigan has a higher cardiovascular death rate than the United States overall. We urge the Board of Governors to direct the university's cardiovascular research program away from the use of what appear to be cruel and scientifically flawed canine experiments and toward human-relevant efforts.

Given the obligation of Wayne State University to "improve the overall health of the community" [60], cardiovascular research should provide a better health return on investment that can be measured in advances in the understanding, prevention, and treatment of human cardiovascular diseases. In our judgment, Dr. O'Leary's dog experiments have not contributed to this purpose and should be ended.

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