



Milestones in Veterinary Cardiology—Past, Present, and Future. Perspective of a Relic

Robert L. Hamlin, DVM, PhD, Diplomate ACVIM (Cardiology, Internal Medicine)
The Ohio State University

The year I graduated from veterinary school, 1958, there was no need for the subspecialty of veterinary cardiology; we recognized only a very few cardiovascular diseases (e.g., fibrosis of the AV valves, patent ductus arteriosus, pulmonic stenosis) and we had only whole leaf tincture of digitalis, meralluride, and nux vomica. Somebody^a said that ventricular arrhythmias in dogs and cats, and heart disease in the cat are extremely rare. Among the things of which we were certain^b was: 1) a failing heart was over distended so that it functioned on the descending limb of the Starling (Frank was added after that time) curve^c; 2) depolarization resulted from sodium ions rushing into the cells and repolarization from sodium ions rushing out of the cells^d; and 3) retention of fluid resulting in edema occurred because of either renal venous hypertension or decreased glomerular filtration rate^e. We had no idea that 1) internal structures could be bombarded with sound waves which, when reflected, permit a repetitive, non-invasive study of structure and motion of the heart, blood vessels and blood itself; 2) genes could be installed into growing cells to alter their longevity and function; and 3) drugs could be used to modify vascular function and decrease both the work of the heart and probably the degree of mitral regurgitation.

So many valuable and exciting things happened in veterinary cardiology during the past 30 years! Certainly this brief review of milestones must begin by acknowledging the father of veterinary cardiology, David Detweiler. His development of the Comparative Cardiovascular Studies Unit at the University of Pennsylvania nurtured some of the finest minds in our specialty and contributed monumentally to our knowledge. Following David Detweiler by only a few years was Charles Roger Smith, a person to whom I personally owe thanks for his brilliance, kindness and ability to impart skillfully and clearly (and with refreshing humility) the rigors of cardiovascular pathophysiology. While much of the early work in veterinary cardiology progressed in Philadelphia and Columbus, others were making real contributions. In Great Britain, Dr. J. Holmes and his graduate students were elucidating fascinating aspects of equine cardiovascular function and disease; his reports would soon be supplemented by the important clinical observations of Fred Fregin and Ginny Reef at New Bolton Center. In New York, Dr. Stephen Ettinger was firmly establishing the clinical specialty of veterinary cardiology in small animal patients and a number of prominent veterinary cardiologists began practicing in universities and eventually in the private sector.

Of course, many others have made important contributions to our understanding of clinical cardiology in companion animals. A few of these people are speaking to you at this very symposium, and it will be my pleasure to single them out (and no doubt embarrass them a bit!) as I point out some highlights in the development of veterinary cardiology. This enumeration is not in any sense encyclopedic, and I apologize at the outset for omitting what may be equally important contributions from colleagues at many other institutions.

For many years, veterinarians examined patients with only their hands, a stethoscope, and radiograph. Many of the early studies in cardiovascular diagnosis – including those of David Detweiler and Don Patterson in Philadelphia and of those in our own “Biology of the Heart” team (which included C. Roger Smith and David Smetzer), concentrated on characterization of heart sounds and murmurs and on basic electrocardiography in small and large animals. Eventually the electrocardiogram became established as an important diagnostic study in veterinary cardiology with many investigators publishing on normal values in various species. The EKG was popularized however by the publications and lectures of Steve Ettinger, Gary Bolton and Larry Tilley; these clinicians also brought our attention to the frequency of various rhythm and conduction disturbances. While



many of us studied the correlative anatomy between radiographs and angiocardiograms, Peter Suter and Peter Lord eventually taught us all how to interpret thoracic radiographs in dogs and cats.

Echocardiography perhaps represents the greatest breakthrough in the field of diagnostic cardiology. B- and M-mode echocardiography, followed by 2-D, Doppler, and color-Doppler, and backscatter analysis to characterize myocardium emerged as a tool most valuable for identifying lesions, studying normal and pathological physiology, in particular to evaluate pericardial disease and ventricular function. Frank Pipers' first papers on veterinary echocardiography must stand out as monumental contributions to veterinary cardiology. In particular the excellent illustrations from Bill Thomas and Sydney Moise are universally referenced for the dog and cat. The echo-Doppler studies in horses by Virginia Reef and John Bonagura are clear benchmarks in veterinary cardiology. The Atlas published by Peter Darke, John Bonagura, and Don Kelley contain outstanding illustrations and verbal descriptions of the clinical applications of echocardiography in small animal practice. The elucidation of echocardiographic standardizations and quantitation by Bill Thomas, Mike O'Grady, David Sisson and many others are important. The concept of "diastology" popularized in veterinary cardiology by Virginia Luis-Fuentes and Karsten Schober, fits well with current thinking that pulmonary edema is more a consequence of diastolic malfunction than systolic malfunction.

A number of important contributions have been made in our understanding of diagnosis and management of spontaneous cardiovascular diseases in cats. Surely, the discovery of taurine deficiency as the major cause of dilated cardiomyopathy in cats (by Paul Pion, Mark Kittleson, Quinton Rogers, and colleagues) represents a landmark study of reversible, nutritionally based cardiomyopathy. Sam Liu's detailed descriptions of the pathology of feline cardiomyopathy conducted during his many years at the Animal Medical Center are equally important. Dr. Liu's clear understanding that thromboembolism in cats was associated with cardiomyopathy, ranks high in importance, particularly to those of us who saw so many cats with saddle thrombi and never associated them with heart disease. The clinical descriptions of feline cardiomyopathy by Neil Harpster in Boston, and by Larry Tilley, Peter Lord, and Phil Fox in New York stand as benchmarks to our understanding of these important syndromes. The studies of feline (and canine) hypertension by Cowgill et al introduced us to a disease of potentially great importance that was virtually ignored previously. The comprehensive descriptions by Clarke Atkins of the interactions of the heart with other organ systems are enormously useful.

Many of my colleagues have taken an interest in myocardial diseases in dogs. Bruce Keene's observations on l-carnitine deficiency as a cause of dilated cardiomyopathy – although not relevant to the majority of dogs affected with cardiomyopathy – is of enormous significance to those dogs that are l-carnitine deficient and who make magical recoveries with l-carnitine supplementation. Similarly, while not many German shepherd puppies demonstrate "puppy" tachycardia, Sydney Moise's encyclopedic description of the pathophysiology of that abnormality stands as a significant contribution and as an important a model of VT for our medical colleagues. Neil Harpster's original classification of "Boxer cardiomyopathy" is still much used in this important disease, and Kate Meurs' clinical trials on Holter monitoring and antiarrhythmic treatment in Boxers with this disease have proven most valuable. The studies by Mike O'Grady and of Clay Calvert regarding the prodromata of dilated cardiomyopathy in Doberman pinchers is of great importance as are Bill Muir's description of the pathophysiology of ventricular arrhythmias associated with gastric distension and torsion.

We have learned much of the genetic tendency for some congenital and acquired diseases. Of course we are indebted to Don Patterson for his pioneering efforts in veterinary genetics. The writings of Patterson, Buchanan, and Pyle exquisitely demonstrated the pathology, clinical findings, and genetics of aortic stenosis in Newfoundlands, patent ductus arteriosus in poodles, tetralogy of Fallot in Keeshunden, and pulmonary stenosis in beagles. We have also learned much more about degenerative mitral regurgitation from the pathology studies of Whitney and Buchanan and more recently from the innovative investigations of our Scandinavian colleagues in their studies of hundreds of Cavalier King Charles Spaniels. That many other common diseases are genetic,



and not congenital, is both obvious and important, e.g., “arrhythmic” cardiomyopathy in Boxers, dilated cardiomyopathy in Dobermans, “arrhythmic cardiomyopathy in German shepherd puppies, “sick sinus syndrome” in miniature schnauzers among so many examples. In many ways we have achieved high levels of expertise in noninvasive cardiac diagnosis, it now remains for the cardiologist-geneticist to help us predict and manage heart diseases in new and novel ways.

While we wait for “gene therapy,” we are still given the opportunity to intervene in a number of meaningful ways. Veterinary anesthesia has progressed to the degree that animals may be anesthetized safely for both diagnostic tests and surgical or catheter treatments of many defects. We install cardiac pacemakers to treat bradyarrhythmias and to synchronize ventricular myocardium when intraventricular conduction disturbances exist. We are now diagnosing and treating re-entrant supraventricular tachycardias with ablation of bypass tracts (following detailed electrophysiological testing). A number of conditions can be improved or even cured with cardiac surgery as nicely demonstrated by pioneering veterinary surgeons Buchanan, Eyster, and Breznock. Today open-heart surgery is a reality (though perhaps a still too-costly one), as Chris Orton has shown us. Catheter-based treatments can be applied to veterinary patients as Matt Miller and others have shown in their application of the Gianturco coil for minimally invasive correction of patent ductus arteriosus. Balloon valvuloplasty of tight pulmonic stenosis is a routine procedure in referral hospitals.

On the medical side there have been many advances since our initial use of digitalis and the sodium-restricted diet. Chemoprophylaxis against heartworm disease in both dogs and cats has progressed so that it is totally unnecessary for a dog to ever die or become incapacitated from this parasite. We have certainly progressed from the days when Ron Jackson taught us about his extensive practice experience with heartworm disease! Complex arrhythmias are managed effectively in many cases with antiarrhythmic drugs and objective measures of treatment generated by ambulatory ECG monitoring. The only blinded clinical trial of a veterinary cardiovascular drug – orchestrated by Tony Benitz and supported by Merck – must stand out as a first for obtaining an FDA label of safety and efficacy for a drug used to canine treat heart failure. This study serves as a template for further clinical trials. Of course, as mentioned previously, heartworm prophylaxis and treatment are approved, however the sophistication of clinical trials required to prove efficacy for prevention and treatment of parasites is trivial compared to that required when end-points of therapy – as for heart failure – are so ethereal^f.

Some organizations have helped advance our general understanding of companion animal disease. The College of Veterinary Internal Medicine with the Specialty in Cardiology has contributed significantly to improving the quality of treatment of heart disease in animals, standardized educational – in particular residency – programs, and provided a journal for publishing reviewed manuscripts, and for meetings to exchange knowledge among cardiologists and non-specialists. It would be impossible to forget the “internationalization” of veterinary cardiology, as the major contributions from our colleagues in Europe, Asia and Australia are continuously added to our literature, and with their participation in national and international meetings on veterinary cardiology.

We recognize that infrahuman mammals have different physiology^g, pathophysiology^h, and pharmacodynamicsⁱ than humans, but instead of learning from infrahuman mammals and extrapolating to humans^j, we are now carrying into our clinics information learned (and paid for by the NIH and 3rd party payers) from humans^k. We also recognize the unique physiology, pathophysiology and pharmacodynamics based upon breed, age, and sex of species treated by the veterinarian.

We have been introduced to terms such as remodeling, inodilators, ryanodine channels, torsades de pointes, sensitivity, specificity, predictive values, meta-analysis, survival curves, proportional hazard, Bland-Altman plot, Fisher’s exact t, and power analysis. These terms have made our profession more precise yet exponentially more complex.

We have been “crushed” by the untimely deaths of our valued colleagues: Gary Bolton, Grant Knowlen, Gerry Rubin, Gene Musselman, David Knight, John-Carl Goodwin. Who can forget their contributions—Gary’s gentle tutoring mixed with cacophonous mimicking of sonorous rhonchi and of course his first textbook on veterinary electrocardiology; Grant’s description of aortic input impedance; Gerry’s wisdom about left atrial tears and apexcardiography; Gene’s popularization of vectorcardiography and that provocative query about “how many faeries can dance on the head of a pin?;” John-Karl’s studies of cardiovascular drugs practice; and Dave Knight’s monumental contributions to the study and treatment of heartworm disease (as well as his demands for rigor in proof of therapy)?

Textbooks in our subspecialty have evolved from Steve Ettinger’s and Peter Suter’s original *Canine Cardiology* to Larry Tilley’s textbook on electrocardiology, to various manuals and series volumes about cardiology, to highly comprehensive textbooks of small animal cardiology authored by Phil Fox, Dave Sisson and Sydney Moise and by Mark Kittleson and Richard Kienle. Although not devoted solely to cardiology, John Bonagura’s *Kirk’s Current Veterinary Therapy*, Steve Ettinger’s *Textbook Veterinary Internal Medicine*, and Larry Tilley and Frank Smith’s *5-Minute Veterinary Consult* place cardiology within the reach of the generalist.

All of the above is history, all but the deaths have been good; but what’s left to do? What are the holes? Why is it that we have only a single drug—enalapril¹—on file with the FDA as safe and efficacious for treatment of heart disease in dogs... and none in cats? Digitalis and furosemide are approved, but without proof of safety or efficacy. Why is it that we do not have criteria, based upon evidence, for precisely when and if, to treat ventricular arrhythmias? Will we ever know which cardiomyopathic cats should be treated with nothing, beta blockers, calcium channels blockers, and/or ACE-inhibitors... alone or in combination? What are the criteria for exactly when—and with what—to treat mitral regurgitation or dilated cardiomyopathy? How many multicenter clinical trials have been conducted to establish safety and efficacy, or even the correct dose? Although it may be medically proper, I truthfully doubt that the dose-range for furosemide should be between 1 and 4 mg/kg from q6h to q8h—a 12-fold range!

What is the normal blood pressure in cats and dogs? What is the influence of age, sex and breed? What is the “white coat” influence? How many normal cats have been studied by echo to determine normal limits for wall thickness? And how was normalcy confirmed? What are the sensitivity and specificity of echocardiography for identifying hypertrophic cardiomyopathy in cats? How many ventricular premature depolarizations, and of what form, are considered normal in Boxers... or any other breed? Should a systolic murmur auscultated in a young Golden Retriever be interpreted differently from the same murmur heard in a young Cocker Spaniel? From where do all of the “Doppler-silent” murmurs arise in cats? What degree of mitral and/or tricuspid regurgitation identified by Doppler interrogation in horses and dogs is normal?

Have we forsaken electrocardiography? If we spent half the time on electrocardiography as on echocardiography, could the ECG become useful for quantifying and prognosticating cardiovascular events? Is “lone” atrial fibrillation in horses really innocent? Why are there no ECG criteria for identifying atrial or ventricular enlargement in animals with more complete penetration of Purkinje fibers? Is it true that electrocardiographic criteria for identifying left ventricular hypertrophy in dogs and cats is so bad as compared with humans? Why, despite evidence to the value of thoracic leads, do so few veterinarians obtain thoracic leads? How many of us are bothered by these questions, and if so, what are we doing to rectify our inadequacies?

Zbinden is arguably the greatest toxicologist that has ever lived. He said that no test should be conducted—and I add no drug should be given—unless there is a reasonable expectation that it will change the outcome of the case. For the benefit of the veterinary cardiologist, we should also add that a test might be ordered if it aids in informing the owner about the predicted quality and duration of life. Should obtaining a test, for the purpose of gratifying the veterinarian’s intellectual curiosity, be paid for by the client? Is it appropriate to treat severe heart failure with the goal of squeezing two more weeks or another month of life from the patient? Do our egos

influence when and with what vigor we recommend euthanasia? Are we too smart to allow an animal to die? Even if a client wants “everything done”^m to prolong their pet’s life even 1 day, is our allegiance to the client or to the pet? Do we have criteria for recommending euthanasia?

I feel certain that veterinary cardiologists are in it for the challenges to make correct diagnoses, for the rewards of prolonging lives with reasonable comfort, for the “thank you” notes written because a pet survived or, if it didn’t, for what we did to help, and to gain knowledge to pass on to future generations. These are fine goals to which most aspire with good humor and great diligence. One of the bad things about being old enough to be asked to write about milestones, is knowing you won’t be around to see what promises to be milestones of the future that dwarf those of the past.

Editor’s note: Of course, Dr. Robert Hamlin has given far too much credit to his colleagues and many trainees, and failed to mention his own numerous and important contributions to the field of veterinary cardiology. Dr. Hamlin has studied, lectured and written about comparative cardiology and clinical veterinary cardiology and pharmacology for over 30 years. While his manuscripts and professional accomplishments are most laudable, those who know him stand in awe at the impact he has created by stimulating and guiding others as they pursued careers in cardiology and cardiovascular science. There are **hundreds** of cardiologists and scientists (and certainly thousands of practicing veterinarians) around the world who can point to the brilliant and approachable Bob Hamlin as their teacher, mentor, colleague, and friend.

J Bonagura, DVM, Columbus, Ohio.

ENDNOTES

- a. Unfortunately, it was the person whose writing you are reading now!
- b. All proven to be false!
- c. Of course, we now know that the heart probably never functions on the descending limb of the curve, but rather functions on another curve.
- d. We now know that repolarization occurs when potassium ions exit up to 15 different channels.
- e. Now we know that renal conservation of salt and water arises from neuroendocrine disturbances and from an **increase** in filtration fraction.
- f. It is rather easy to count parasites, but end-points for treating of heart failure – other than death – are difficult to assess!
- g. Pronounced respiratory sinus arrhythmia in dogs, S3 gallops, 2nd degree AV block, and bifid P waves in horses
- h. Only man develops atherosclerosis of extramural coronary arteries, prevalence of mitral regurgitation in dogs is much higher than in man, subaortic stenosis is much more prevalent in dogs than in man.
- i. ACEinhibitors rarely cause coughs in infrahuman animals dogs, adenosine has virtually no bradycardic effect in dogs, amiodarone rarely produces corneal deposits in dogs, sensitivity of dogs to doxorubicin.
- j. Surgical techniques, drug safety, mechanisms and treatment of arrhythmias.
- k. Reduction in afterload, improving quality and duration of life with ACE inhibitors, spironolactone and carvedilol.
- l. Of course, drugs are approved, as well, for prevention and treatment of heartworm disease.
- m. “Spare no expense!”



Notes

Copyright © 2002 All Rights Reserved

Waltham USA, Inc

The Ohio State University, College of Veterinary Medicine

All rights including that of translation into other languages, reserved. Photomechanical reproduction (photocopy, microcopy) of this publication or parts thereof without written permission from Waltham USA, Inc. is prohibited. The opinions expressed in these proceedings are those of the authors and not necessarily those of Waltham USA, Inc.