ADVANCES IN CANINE CARDIOLOGY: OVERVIEW

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For many years, veterinarians examined patients with only their hands, a stethoscope, and radiogra -ph. Many of the early studies in cardiovascular diagnosis concentrated on characterization of heart sounds and murmurs arid on basic electrocardiography in small and large animals. Eventually the electrocardiogra -m became established as an important diagnostic study in veterinary cardiology with many investigators publishing on normal values in various species. These clinicians also brought our attention to the frequency of various rhythm and conduction disturbances.

So many valuable and exciting things happened in veterinary cardiology during the past 30 years! 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.

A number of important contributions have been made in our understanding of diagnosis and manag -ement of spontaneous cardiovascular diseases in dogs and cats. The following paragraphs deal briefly about the various advances in small animal cardiology.

Diagnostic Advances

Intravascular ultrasound in coronary atherosclerosis

Intravascular ultrasound evaluation of the coronary arteries by means of a selective coronary cathet -er attached to an ultrasound unit has afforded precise depiction of coronary lumen diameter and area at the level of the catheter tip. The arterial wall at this level can be evaluated for lipid, fibrous tissue, calcification, wall dissections, and intraluminal thrombi. The technique has the advantage over coronary angioscopy and angiography in that it does not require infusions or injections to allow visualization, and it has the ability to depict the inside of the arterial wall. The current disadvantages include the inability to visualize the vessel segments distal to the catheter tip. Three-dimensional reconstruction techniques allow depiction of the segment of the artery traversed by the catheter tip. The use of Doppler ultrasound imaging provides informa -tion on coronary flow velocities through coronary obstructions. Intravascular ultrasound images may provide information that complements the coronary arteriogram and may have an impact on patient care and clinical investigation strategies.

Doppler echocardiography

M-mode and two-dimensional echocardiography (2DE) are standard parts of the evaluation of cardi -ac structure and function in veterinary and human cardiology. Doppler echocardiography, although consid -ered standard in human cardiology, is in its infancy in veterinary cardiology. It is becoming an important non-invasive component of the evaluation of cardiac patients since it adds information formerly only available from cardiac catheterization. Specifically, it can analyze blood flow direction, character, velocity, and timing. Like M-mode and 2DE, this safe, non-invasive technique is ideal for serial evaluation of patient -s with heart disease. Although useful in both congenital and acquired heart disease, in our hospital it has primarily been used to evaluate congenital heart defects.

In vivo diagnostic and therapeutic uses of monoclonal antibodies in cardiology

Antibodies, long used as discriminating tools in immunoassay, are now being used in vivo, both in diagnosis and therapy. In cardiovascular medicine, applications that have reached the stage of clinical trial include the reversal of digitalis intoxication by digoxin-specific antibodies and the imaging of cardiac necro -sis with monoclonal myosin-specific antibodies. An exciting future prospect, still in an early experimental stage, is the application of fibrin-specific monoclonal antibodies to both the visualization of thrombi and emboli and the targeting of fibrinolytic agents.

CT scanning of the heart

It is generally agreed that all present diagnostiC cardiac methods including

echocardiography, nuclear medicine, and coronary arteriography have significant limitations. Nuclear cardiology provides excellent diagnostic sensitivity using small amounts of radioactive tracers, but it currently lacks the spatial fidelity needed to differentiate many anatomic structures in the heart. CT complements the capabilities of these alternative imaging modalities. Computed tomography offers accurate reconstruction of the whole myocardium with far greater spatial and density resolution in three dimensions. CT may eventually find its most important and clinically useful application in the diagnosis and management of heart disease.

Cardiovascular nuclear medicine

Some of the available cardiovascular nuclear medicine methods are incompletely validated, and others are incompletely developed. They are, however, of very great potential in diagnostic cardiology, and in patient management. A new era of clinical research and acute care monitoring has been opened by serial, noninvasive, hemodynamic measurements of right ventricular as well as left ventricular function. Stress test -ing has become more specific, and should, with future developments, become more specific, and should, with future developments, become more sensitive, using radionuclide procedures. Serious quality control and validation questions concerning thallium stress testing must be addressed. Intracoronary injection of radiogases has great potential, although minimal present application. Emission computerized tomography will be an important research tool. Compartmental analysis modeling of first pass tracer injections has much to offer, but is not yet validated. Present growth rate of these procedures is very rapid. Fully developed, cardiovascular nuclear medicine may become the largest component of clinical nuclear medicine practice.

Catheter assessment of coronary blood flow and myocardial perfusion

Recent advances in interventional cardiology have pointed out substantial limitations of traditional arteriography in assessing coronary artery anatomy and physiology, especially during the dilatation proce-ss. Numerous new techniques are currently being developed to allow visualization of luminal and mural processes, parameters of relative and absolute coronary blood flow, regional myocardial perfusion, and regions of risk. It is possible that the analysis of coronary cross-sectional area may be performed in the future using nonangiographic techniques. The legitimate diagnostic demands and widespread use of corona -ry angioplasty make it likely that the more promising of these techniques will be clinically available in the near future.

Finding cardiovascular disease genes in the dog

Recent advances in canine genomics are changing the landscape of veterinary biology, and by default, veterinary medicine. No longer are clinicians locked into traditional methods of diagnoses and therapy. Rather, major advances in canine genetiCS and genomics from the past five years are now changin -g the way the veterinarian of the 21st century practices medicine. First, the availability of a dense genome map gives canine genetics a much-needed foothold in comparative medicine, allowing advances made in human and mouse genetics to be applied to companion animals. Second, the recently released 7.5x whole genome sequence of the dog is facilitatinq the identification of hereditary disease genes. Finally, developm -ent of genetic tools for rapid screening of families and populations at risk for inherited disease means that the cost of identifying and testing for disease loci will significantly decrease in coming years. Out of these advances will come major changes in companion animal diagnostics and therapy? Clinicians will be able to offer their clients genetic testing and counseling for a myriad of disorders. In this review we summarize recent findings in canine genomics and discuss their application to the study of canine cardiac health.

Biochemical Markers of Cardiac Dysfunction

Biochemical screening for heart disease in certain defined pet populations using natriuretic peptide, endothelin, or troponin assays is an attractive hypothesis. The prospect of identifying dogs (and cats) with asymptomatic heart disease via biochemical testing is exciting from several perspectives. First, it would likely permit individuals without extensive training in cardiology to identify animals with heart disea -se more accurately and at an earlier point in time. Such testing

could facilitate the delivery of medical treatment at an earlier stage of the disease process than is currently accomplished while avoiding unnecessary treatment of unaffected or mildly affected animals. Biochemical testing might also help clarify the status of dogs with equivocal results when evaluated by other diagnostic modalities, e.g., dogs with "cardiomegaly" on thoracic radiographs or large breed dogs with mildly reduced contractile indices on an echocardiogram. Some obvious applications might include screening the breeding populations of cats for hypertrophic cardiomyopathy and asymptomatic Doberman pinschers for dilated cardiomyopathy. For screening purposes, a test must have very high sensitivity; i.e., it should detect at least 90 per cent of the target group(s). It must also have a reasonable level of specificity, as this population of animals will subsequently require additional evaluation, such as echocardiography, at substantial cost to the owner to confirm the diagnosis. The required level of specificity is debatable, but it is reasonable to assume that a useful test would have a specificity exceeding 70 percent.

Advances in Treatment of Heart Failure

Over the past twenty years there has been a dramatic change in approach to the treatment of heart failure. We have progressed from an era where the only drugs available were digoxin and diuretics, to an era where multiple new drugs with different strategies are becoming available. The development of new drugs is partly related to the explosion in our knowledge of the processes involved in heart failure. It is essential that the clinician understands the principal mechanisms underlying congestive heart failure for logical selection of treatment.

Neurohormonal activation

Arterial under-filling leads to production of neurohormones that cause vasoconstriction and/ or sodium and water retention, both of which restore normal arterial pressures but at increased energy cost to the myocardium. Baroreceptor sensitivity is decreased in heart failure, so that although normal arterial pressures are restored, increased sympathetic drive continues. Although heart failure also increases concentrations of some 'beneficial' neurohormones (atrial natriuretic peptide, brain natriuretic peptide), the vasodilatory and natriuretic properties of these hormones tends to be overwhelmed by the effects of the neurohormones mentioned above. An understanding of the importance of neurohormonal mechanisms in heart failure has resulted in some changes to our approach in treatment. Diuretics are still employed for elimination of sodium and water, but ***ACE inhibitors*** have assumed increasing importance. ***Digoxin*** is now used as much for its effects in restoring baroreceptor sensitivity as for its positive inotropic effects.

Ventricular remodeling

Further refinements to the neurohormonal theory of heart failure have shown that there are adverse effects on the myocardium in addition to the increased workload imposed by neurohormonal activation. These are local tissue effects, whereby the structure and function of the myocardium itself is altered by neurohormo-nes. In vivo, catecholamines contribute to myocyte loss. There are a number of mechanisms that attempt to limit the effect of catecholamines on the myocardium, such as beta-receptor down-regulatio -n. Other neurohormones also have direct tissue effects: angiotensin II and aldosterone promote interstitial fibrosis. The net result is a decrease in diastolic and systolic function attributable to the effects of neurohor -mones, independent of the initial cardiac lesion. The heart dilates, and becomes less efficient mechanically leading to further worsening of cardiac function and further neurohormonal activation. However, therapy directed at reducing remodeling (e.g., beta-adrenergic antagonists) sometimes has adverse short-term hemodynamic effects. Therapy aimed at reducing neurohormonal activation in general will be expected to help reduce progression of ventricular remodeling.

Implications for treatment of heart failure

The aims of acute therapy of heart failure are clearly different from the therapy of chronic heart failure. Acute therapy must concentrate on preventing death from hypoxia, and improving hemodynamics. The effects on neurohormones are not so important in the short-term.

The goal of chronic therapy is to remove excess sodium and water retention, and modulating harmful neurohormones so that congestive signs are less likely. Ideally, therapy should help to limit the effects of ventricular remodeling. Drugs that result in neurohormonal

activation (dobutamine, hydralazine) are best avoided. However, drugs that directly limit sympathetic drive (i.e., beta-adrenergic antagonists) are difficult to use, because they cause a direct fall in cardiac output in the short-term and are poorly tolerated. Their use has not been studied in naturally occurring heart disease in dogs. An alternative approach is to use pimobendan to increase cardiac output, which rather than causing neurohormonal activation, may actually decrease neurohormones indirectly.

Acute Therapy

•	Treat hypoxia	•	Oxygen
•	Drain pleural effusions	•	Atrial pressures
•	Furosemide	•	Venodilators (nitroglycerine)
•	Cardiac output	•	(Dobutamine)
•	Pimobendan		

Chronic Therapy

• Na+ and H20 retention
• Neurohormones
• Spironolactone
• Cardiac output

• Furosemide
• ACE inhibitors
• ? Digoxin
• Pimobendan

Newer Heart Failure Therapy *Pimobendan*

Most positive inotropes increase the cytosolic concentration of calcium to increase the availability of calcium, but pimobendan has the novel action of increasing the sensitivity of the contractile proteins to calcium, an effect thought to be mediated by altering the binding of calcium to the troponin complex, and the increase in the extent of sarcomere shortening is achieved without the same energy consumption associated with sympathomimetic drugs. Pimobendan has both calcium sensitizing effects and some phosph - odiesterase inhibitory effects. The calcium sensitizing effects appear to predominate in failing myocardium because of down-regulation of the adrenergic signaling pathway. The phosphodiesterase inhibition also results in vasodilation. Phosphodiesterases are involved in the breakdown of cAMP in vascular smooth muscle, and inhibitors of these phosphodiesterases will cause venodilation and arteriodilation. There has been no significant increase in mortality in clinical human studies, and neurohormonal activation appears to be reduced with its use.

Pimobendan is available as an oral preparation, and can be used in both acute and chronic heart failure. In acute heart failure it can be used in place of positive inotrope infusions, and will increase cardiac output and decrease filling pressures. Normally hypotension is not a problem because of concurrent augme -ntation of contractility, although blood pressure should be monitored. At normal dose rates of 0.1-0.3 mg/kg q 12 hours it should not affect heart rate and is not arrhythmogenic. In chronic heart failure, it can be used long-term to increase contractility without causing neurohormonal activation.

Spironolactone

Spironolactone is not a new treatment, but its use has recently been reevaluated in human heart failure patients. Once thought of only as a potassium-sparing diuretic, it is now viewed as a useful adjunct to countering the renin-angiotensin-aldosterone system. Aldosterone not only has adverse cardiovascular effects by leading to sodium and water retention, but also has directly harmful myocardial tissue effects.

Beta-adrenergic antagonists

Attitudes towards beta-blockade in the field of human dilated cardiomyopathy have undergone dramatic changes in the past 10 years. Beta-adrenergic blockers have traditionally been considered to be contraindicated in myocardial failure, because of their adverse acute hemodynamic effects. It now appears that long-term use of beta-adrenergic antagonists (>3 months) is associated with improvement in systolic function in human patients, an effect which seems paradoxical, as the short-term hemodynamic effects are negatively inotropic. It was initially believed that the mechanism was related to reversal of the down-regulation of rs-receptors that occurs with chronically

elevated catecholamine levels; however, some beta-adrenergic blockers, produce an improvement in systolic function without causing any !1-receptor up-regulation. It now appears that the improvement is related to an increase in contractile function in the cardiac myocytes themselves, which may be a result of an increase in contractile elements. Certain strict
guidelines are recommended for commencing therapy with beta-adrenergic antagonists in human patients with myocardial failure:

patients must be stable and compensated (i.e., no congestive sign's); doses must be extremely low initially (often < 0.1 of target dose); and doses must be titrated upwards slowly (at 1-2 week intervals). The introduction of beta-blockers with concurrent alpha-1 adrenergic blocking effects (such as carvedilol) has led to improved tolerance in heart failure patients, as the vasodilatory effects offset the decrease in stroke volume associated with the negative inotropic effects.

To date, there have been no reported studies of the effects of beta-blockade on systolic function in dogs with naturally occurring heart disease, although one study in dogs with experimental mitral regurgit -ation did show an improvement in contractile function of isolated cardiomyocytes following atenolol therapy. In the absence of further data, it is speculative whether beta-blockers will eventually have a place in treatment of canine myocardial failure. Problems with canine patients include the long titration period required before beneficial effects might be seen: unless the projected survival time exceeds 3 months, there is little point in starting a beta-blocker for its long term effects. Furthermore, human patients often report feeling worse before they feel better with beta-blockers, and this short-term effect may be difficult to justify in dogs with OCM. At present, the use of beta-blockers in canine OCM is certainly indicated for heart rate control in atrial fibrillation (in conjunction with digoxin) or antiarrhythmic therapy for ventricular arrhythm -ias, but there are no recommended guidelines for use in dogs with DCM and controlled heart failure. Clinical studies are currently underway to investigate use of carvedilol in canine heart failure.

Critical care cardiology

Emergency management of the patient with cardiac disease is an important part of veterinary practice. Although the causes of cardiac disease may be diverse, the understanding of basic pathophysiolog -y will enable the clinician to formulate a rational diagnostic and therapeutic plan. The veterinary clinician must be able to triage the emergency patient, assess the clinical condition, and provide appropriate therapy. Close monitoring of the critically ill patient is crucial to patient survival and will help tailor therapy.

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