



**Review Paper**  
**Heart Failure in Small Animals - Advances in  
Clinical Case Management**

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**SUMMARY**

The rationale for the use of drugs and supportive therapy in the management of heart diseases (HDs) and heart failure (HF), is discussed in the light of contemporary concepts. The inadequacy of the age-long therapy of heart failure with oxygen supplementation, cardiac glycosides, rest and the withholding of salt in food is explained. The weaknesses of certain agents in the management of HF, particularly their inability to halt or reverse pre-existing pathologies, is also briefly discussed. The irreversible nature and the eventual fatal termination from HF has been attributed to sub-cellular changes or remodelling in the intracellular organelles and extra-cellular tissues of the heart, the blood vessels and possibly other internal organs under the influence of nor-adrenaline, angiotensin II, serotonin, aldosterone, growth hormones and anti-diuretic hormone (ADH). In addition, some of these agents downgrade or alter the functions of bradykinin, nitric acid and natriuretic peptides - hormones essential for normal cardiovascular functions. Some of the newer drugs currently used in the management of HF tend to attenuate the progression of the intra- and extra-cellular changes associated with HF. Others either halt or actually reverse them. Although they do not prevent the eventual fatalities from HF, they tend to prolong the survival periods between the diagnosis of HF and death from it, an outcome which in some circumstances could be of immense importance or benefit.

**Keywords:** Management, Heart Failure, Small Animals

**INTRODUCTION**

The use of diuretics, cardiac glycosides and oxygen supplementation, withholding of salt in the diet, and rest has been the standard therapy for HF in man and animals for several decades. Unfortunately, most HF patients become refractive to this therapy and die from HF on the long run (Fox, 1994; Boswood, 2007). This is because the therapy does not alter, attenuate or halt the sub-cellular remodelling and/or pathological changes associated with HDs and HF. Also it does not reverse the highly malleable but resilient neuro-humoral system which initiates, sustains and controls these intra- and extra cellular changes (remodelling) and dysfunctions seen in several organs in HF. The general experience in the treatment of HF in man and animals is that once a HD progresses to HF, it is impossible to restore the patient completely to normal health. This is so, even if the ailing heart is replaced with a completely healthy one or restored to normal therapeutically or if the associated vascular and systemic pathologies are reversed (Hamlin *et al.*, 1994).

The newer drugs which are currently used in the management of HDs and HF in animals and man have been developed following a better understanding of the pathogenesis of HF. They interfere, in some ways, with the actions of catecholamines, angiotensin conversion enzymes (ACEs), aldosterone, anti-diuretic hormone and others incriminated in the

pathogenesis of HF. Therefore, the new drugs now used in the treatment of HDs and HF are vasodilators, angiotensin conversion enzymes inhibitors (ACEIs), more effective and efficient inotropic drugs, medications that cause better or normalised calcium ion trans-membrane transfer and/or metabolism,  $\beta$ -adrenergic receptor blockers, calcium ion channel blockers and angiotensin II receptor antagonists (Hamlin, 1977; Woods, 1978; Atwell, 1979; McIntosh, 1981; Weirich, 1990; Bulmer and Sisson, 2005). By interfering with the functions of the afore-mentioned endogenous substances, these drugs attempt to attenuate, halt and, in some cases, reverse the remodelling process which the latter cause in the heart and possibly other body organs which are responsible for the temporal progression of HD to HF and, of the later, to fatality. These drugs do not totally prevent the progression of HDs to, or alter the ultimate death rates from HF. They however, provide alleviation from severe clinical signs, provide a better quality of life for the patient and may prolong survival intervals between diagnosis of, and fatality from HF by up to one hundred percent (100%) over the results of treatment by the older therapy (Gordon, 2004; Bulmer and Sisson, 2005; O'Grady, *et al.*, 2007; Wolley, *et al.*, 2007).

#### **Management of Heart Failure in Small Animals**

For appropriate and adequate management, HDs and HF should be classified into congenital or acquired, acute or chronic, left or right sided, diastolic, systolic or mixed, into phases Ia, Ib, II or III (ISACHC scheme) and whether they are amenable to medical or surgical therapy or not (Fig I). It is also very important to identify the primary cause(s) of the HD or HF such as atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), sub-aortic valvular stenosis (SAS), mitral valve insufficiency (MVI) or dirofilariasis to enable the clinician formulate the appropriate

treatment tailored to the needs of the individual patient (Häggström *et al.*, 2009).

Until quite recently, it was generally felt that animals with HDs i.e. phases Ia and Ib HF according to the International Small Animal Cardiac Health Council (ISACHC) classification, should not be treated at all except for the restriction of exercise or exertion. This was because no treatment had been equivocally shown to prevent or delay the progression of HDs to HF in man or animals. In fact, treatment of such cases was not only thought to be contraindicated but possibly harmful (Wood, 1978). Definitive treatment of HDs was considered necessary only for congenital cardio-vascular defects which might progress to HF later. Other cases of HDs were managed with enforced rest and careful and close monitoring so that any signs of progression to HF (phase II) were identified early so that prompt and appropriate management procedures could be instituted as necessary. Recent evidence and limited clinical trials would appear, to suggest though rather inconclusively, that in addition to enforced rest, low doses of angiotensin conversion enzymes inhibitors (ACEIs) and in particular enalapril, veno- or iono-dilators like prazosin or pimobendan, calcium transport and utilisation modifiers singly or in various combinations may be useful in attenuating the progression of HDs to HF in both humans and Small Animals (Sisson, 1994; Wolley, *et al.*, 2007) and therefore could be of some clinical benefit in cases of HDs.

Generally, the management or treatment of congenital and acquired cardiac conditions resulting in HDs or HF differ fundamentally one from the other. Heart diseases caused by congenital anomalies should be treated as soon as possible provided the patients are in good enough physical and clinical conditions to withstand the appropriate anaesthetic protocols and surgical procedures. In particular, extreme caution should be exercised in anaesthetising and operating on animals with respiratory

distress. Such cases are encountered in cyanotic patients with reversed left to right shunts as in Eisenmenger complex or syndrome even when the respiratory stress has been resolved (Oyema *et al.*, 2005). Most of these conditions in dogs and cats can be treated by extra-cardiac surgical procedures such as pulmonary artery banding for VSD, duct ligation or trans-arterial transplantation of coils for PDA, trans-ventricular forceps or balloon dilation of SAS or PS and circumferential mitral valve purse string suturing (PSS) for MVI (Häggström *et al.*, 2009). Such extra-cardiac procedures do not require cardio-pulmonary by-pass techniques (DeLillis, *et al.*, 1993; Buchanan and Sammarco, 1998). These procedures and others though relatively simple, require specialized equipment and some expertise in intra-thoracic surgical techniques. Valvular replacement, repair of ASD and a few others require cardio-pulmonary by-pass equipment and procedures.

Acute HF caused by severe arrhythmias, ruptured chordae tendinae, cardiac tamponade, severe caval syndrome, severe pleural effusion, aortic thrombo-embolism ATE particularly in cats and atrial stand-still is usually sudden in onset and presents as an emergency. It causes sudden and severe hypotensive hypoperfusion, cardiogenic shock and does not allow the body to recruit the Neuro-humoral compensatory mechanisms before the patient dies. Its management, where possible, is fundamentally different from that of congestive HF. Irrespective of the primary cause(s), the treatment of acute HF is aimed at sustaining life over a brief period and is generally unsuitable for long term or maintenance therapy. Generally, animals in acute HF should be handled carefully, and treatment should be instituted without undue delay once the diagnosis is made if success is to be achieved (Fuentes, 2007; Erling and Mazzaferro, 2008). Animals that are difficult to handle may be sedated lightly with low doses of acepromazine, or medium efficacy opioids like butorphanol or buprenorphine. Oxygen therapy

should be provided by masks, hoods, tents, flow-by or intranasal intubation in the least stressful manner (Erling and Mazzaferro, 2008). Other specific therapies required in specific cases depend on the primary cause(s) of the acute HF (Table 1). For instance acute HF due to ventricular fibrillation responds well to lidocaine or procainamide therapy. In acute HF caused or complicated by pleural effusion or cardiac tamponade, the aseptic withdrawal of small quantities of fluid by thoracentesis or pericardio-centesis can be life saving. Where acute HF is treated successfully it usually progresses to congestive HF (Ettinger *et al.*, 1998).

Congestive HF in Small Animals is caused by a variety of primary cardiac pathologies and may be encountered clinically as HF phase II or III (ISACHC classification). In addition to the basic drug used in the management of all forms of HF, the primary cause(s) of the HF e.g. DCM, RCM, hypertrophic cardiomyopathy (HCM), dirofilariasis, etc influence the choice and effectiveness of any additional measures or medications that may be added for the comprehensive and adequate management of a particular case (Bulmar and Sisson, 2005) (Table 2).

The differences in the mode of management of phase II or III HF depend on the aggressiveness of therapy in terms of drug combinations, dosage and frequencies of administration and other measures adopted for each case.

In chronic HF (Phases II and III) there is a gross mis-match between pulmonary perfusion on the one hand and ventilation and oxygen absorption by pulmonary vessels on the other resulting in low oxygen tension in pulmonary venal blood. In such cases, oxygen supplementation should be delivered through modalities described for acute HF above in order to enhance oxygen availability to and absorption by the blood flowing through the lungs. This is vital in all cases of HF but is critical in left sided HF with pulmonary compromise and with signs of coughing, dyspnoea, orthopnoea and exercise

intolerance such as MVI, myxodematous mitral valve disease (MMVD), severe DCM and reversed

**TABLE 1: Management of acute heart failure in dogs**

CLINICAL CONDITION	SUGGESTED MANAGEMENT PROCEDURE
Excited, Fractious Or	Sedate with acepromazine (0.3mg/kg) or morphine, or butorphanol (.2-.4mg/kg) or buprenorphine (0.02mg/kg) Repeat
Pleural or pericardial effusions	Aseptically perform thoracocentesis or pericardiocentesis. Stabilize, give oxygen supplementation, Place on furosemide if there is evidence of fluid retention in the lungs or in the thoracic and/abdominal cavities.
Hypotension	Debutamine 2.5ug/kg/min, digitalis, adrenaline or nor-adrenaline. Alternatively, start treatment straight away with pimobendan 0.2mg/kg q12h. Oxygen supplementation. Give fluids slowly or plasma expanders until systolic blood pressure rises to about 70mm Hg.
Severe bradycardia	Ensure air passages are patent, administer oxygen supplementation and give atropine sulphate or glycopyrrolate
Atrial standstill	Adminster calcium gluconate or borogluconate slowly at 0.5mls of 10% solution/kg; plus 0.9 sodium chloride i/v
Atrial or supra-ventricular tachycardia	Vagal manouvre (eg inducing the gagging reflex), digitalis, i/v diltiazem or sotalol or i/v lidocaine 0.2-2.0 mg/kg/min ( lower doses for cats)

Adopted from Fuentes, V. L. (2007). Cardiovascular emergencies. 56<sup>th</sup> congress Internationale Multisola SCIVAC. Rimini, 2007, 235-237.

Diuretics therapy should be initiated early and aggressively in phase II or III HF and sustained until the estimated blood volume (90mls/kg for dogs and 70ml/kg for cats) is reduced by seven percent, the body weight is reduced by ten percent of their pre-treatment values or until there is considerable clinical relief from respiratory distress. The most commonly used diuretic in the management of HF is the loop diuretic-furosemide. To achieve the above objectives, furosemide should be administered at either an initial bolus dose of 2.0-4.0 mg per kilogram body weight (mg/kg bwt) two to four hourly intravenously or by constant rate infusion (CRI) at a dose of 0.5-1.0 mg/kg bwt/hr using the smallest non-ionic (glucose or dextrose) fluid volume possible. A fluid flow rate of 2-3 drops/min using a paediatric drip set (2-3mls/hr) has been found to be adequate for this purpose in most cases and keeps the intravenous cannula patent (personal experience). The rationale for administering furosemide by CRI to hyper-volaemic patients with pre-renal azotaemia is to rapidly decongest the co-existing pulmonary congestion/oedema by rapid diuresis. The administration of furosemide by CRI has been reported to produce more consistent diuresis, natriuresis and calciuresis but reduced

kaliuresis than intermittent scheduled bolus dosing (Hägström et al., 2009; Erling and Mazzaferro, 2008). It also circumvents the ionic re-absorption re-bounce that occurs during the intervals between scheduled dosing with furosemide or other diuretics which results in a hypernatremia. The strict adherence to the CRI regimen of diuretic therapy is essential if the benefits of using diuretics for the rapid reduction of pre-load and pulmonary congestion are to be achieved. On long term, patients may become refractory to furosemide therapy irrespective of dosage and mode of administration. In such cases, other types of diuretics such as chlorothiazide (15-20mg/kg body weight) or hydrochlorothiazide (2-4mg/kg body weight) may be administered to such patients. However, diuretics should not be used alone or early in the management of HF as they tend to activate the rennin-angiotensin-aldosterone-system (RAAS) when the blood sodium level is too low and there is a low sodium delivery to the macula densa of the kidneys (Fuentes, 2004).

**Table II: Therapeutic and management protocols for different phases of heart diseases and failure based on phases and classification**

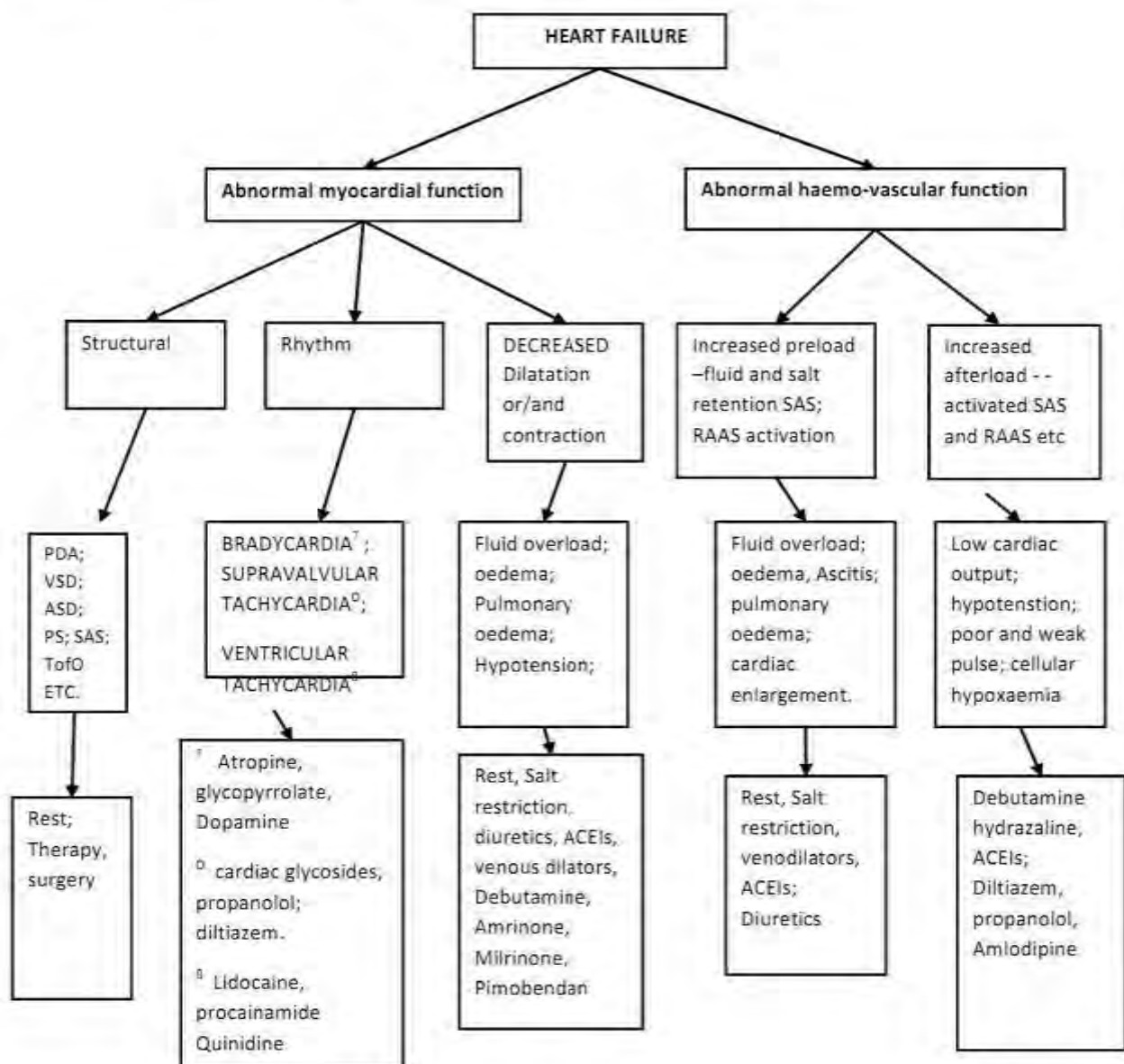
PHASE/ CONDITIO	CLINICO- PATHOLOGICAL	CLINICAL PRESENTATION	AIMS OF THERAPY OR	SUGGESTED AGENTS TO USE
HD Phase Ia	Detectable clinical signs only	Tachycardia, split heart sounds, murmurs, missing pulse.	Reduction of stress	Limit exercise or in latter stages, En-forced rest.
Phase Ib	As in Ia plus cardiac changes	No functional dysfunction As above plus enlarged heart	Reduce stress; forestall activation of SNS and RAAS	O <sub>2</sub> supplement, rest, β- adrenergic blockers, and ACEIs
ABNORMA L RHYTHM Atrial fibrillation	Superactive SA node.	Rapid irregular heart rate, varied intensity of 1st sound; 2 <sup>nd</sup> sound present or absent,	Slow heart rate	Cardiac glycosides, β- adrenergic blockers, Ca ion transport and utilisation modifiers.
Ventricular tachycardia	Active ventricular ectopic foci	Bursts of rapid regular heart sounds that cease suddenly;	Deactivate ventricular foci	Lidocaine; procainamide; quinidine; β-adrenergic blockers.
Bradycardia	Left bundle block; A-V block	split 2 <sup>nd</sup> heart sound	Down grade parasympathet ic tone; stimulate heart	atropine, glycopyrrolate; amrinone, milrinone,
DCM	Diminished contractility	Diminished 1st sound. Audible 4 <sup>th</sup> sound	Strengthen heart, reduce impedence, decrease O <sub>2</sub> demand and enhance use	Milrinone, Amrinone, pimobendan, diltiazine, vasodilators, ACEIs; β- adrenergic blockers; pimobendan

MVI; MMVD;	Enlarged left ventricle and auricle on X-ray and ECG; & ultrasound	Hypokinetic: pulse, weak; systolic murmur, cough, râles; poor oxygenation	Reduce pre- and after-load; Enhance cardiac function	Diuretics; morphine, ACEIs; vasodilators; O <sub>2</sub> supplementation, amrinone, milrinone
HCM and RCM	Inadequate dilation of heart chambers	Backward failure; low CO;	Prolong diastolic phase; Enhance fillig of ventricles	Cardiac glycosides; β-blockers; Ca <sup>++</sup> enhancers , ACEIs-pimobendan
Systolic forward HF; SAS, PS, aortic insufficiency	Low pulse; split 2nd heart sound	Weak; slow rising pulse, dyspnoea, cold extremities, increased capillary refill time	Decrease after load; Relieve stenosis	Arterial dilators; ACEIs; β-blockers; low dose diuretics except phase III; Baloon or forceps dilation.
All HF progressing to phases II or III	Activated SNS and RAAS; Down - graded bradykinin; NO <sub>2</sub> Natriuretic peptides	Weakness at rest; dyspnoea; cough; orthopnoea; oliguria; altered sleep pattern	Decongest lungs, clear respiratory passages; rest Increase CO. Enhance oxygenation	Diuretics (i.v); broncodilators; O <sub>2</sub> supplementation; balanced vaso-dilators; ACEIs;β-blockers; moderate salt restriction (25 - 30mg/kg/day
Structural Defects ASD; VSD; PDA; SAS; PS; TofF	Varied: initial left to right shunts  Later right to left shunt with cyanosis eg Eisenmenger complex	Murmurs, split heart sounds; low pulse pressure; hypokinetic or hyperkinetic pulse; poor growth  DITTO; posterior or generalised cyanosis; cough, dyspnoea due to pulmonary-hypertension	Surgical closure of defects or selective increase of vascular pressure  Ditto but after resolving pulmonary hypertension and pneumonia	PDA-ligation/ coil placement; VSD- pul. artery binding; SAS and PS- circumferential suture  Ditto.

Adopted from Anon. Appendix A: Common Cardiovascular Drugs and Recommended Dosages” In Recommendations for the diagnosis of heart disease and the treatment of heart failure in Small Animals. ISACHC publication. 30-31, 1994.

Note: myxodematous mitral valve degeneration (MMVD), sub-aortic stenosis (SAS), pulmonic stenosis (PS) patent ductus arteriosus (PDA), Tetralogy of Fallot (TOF), ventricular septal defect (VSD), atrial septal defect (ASD), hypertrophic cardio-myopathy (HCM), restrictive cardiomyopathy (RCM), dilated cardio-myopathy (DCM), mitral valve insufficiency (MVI), rennin-angiotensin- aldosterone system (RAAS), CO cardiac output.

Fig: 1. Classification of heart diseases into medical or surgical categories





The objectives of using cardiac glycosides like digitalis are to slow the heart rate, allow for a longer diastolic interval so that the venous return may improve and to enable the ventricular muscles (cardio-myocytes) stretch to their maximum length in order to achieve an enhanced cardiac output in consonance with the Frank-Starlings law of the heart (Guyton and Hall, 2000). However, from a therapeutic view point, cardiac glycosides appear inferior to the synthetic sympathomimetic drugs like debutamine, amrinone and milrinone in increasing cardiac output in cases of HF in humans and small animals. Cardiac glycosides actually cause several undesirable side effects which include increased oxygen demand and consumption by cardio-myocytes, inciting of atrial arrhythmias, vasoconstriction, vomiting, diarrhoea and renal toxicity which together with the difficulties of accurate dosing make them less favoured than the synthetic sympathomimetics (Erling and Mazzaferro, 2008). Their usefulness in the management of HF would now appear to be restricted to cases associated with supra-ventricular tachycardia or arrhythmias.

The withholding of salt in the diet of HF patients as a means of reducing sodium and water load and thereby lowering the blood volume was considered helpful until lately. This practice has been found to be deleterious to the management efforts in HF. Firstly; lack of salt in the diet makes the food less palatable, reduces the animal's appetite and increases the anorexia in the already sick animal. It, like the loop diuretics, also induces the release of rennin from the juxtaglomerular apparatus by the induced low sodium delivery to the macula densa of the kidneys early in the pathogenesis of HD. This triggers off an early production of angiotensin II during the pathogenesis of HDs (Boswood, 2007). Therefore the complete withholding of salt from the diet of HD and HF patient has given way to the graded reduction in the quantity of salt in the food of such patients depending on their phase of HF. (Woods, 1978;

Boswood, 2007). Ideally, some moderate amount of salt (30mg/kg/day) can be added to the food of phase II HF patients. Only phase III HF patients need have their food prepared with severe reduction in the salt content (20-24mg/kg/day) (Bulmer and Sisson, 2005)

The above measures put together, attempt to reverse the adverse effects of the compensatory responses of several body systems to a failing heart but not the structural changes in the heart and several organs which need to be halted and at best reversed. Secondly the sympathetic nervous system (SNS) and the RAAS which remain activated need to be de-activated. Failing these, patients suffering from HF eventually become refractory to the above regimen and may die within six to twelve months following the diagnosis of HF even if the above therapy has been instituted. (Boswood, 2007).

Arising from a better understanding of the patho-physiology of HDs and HF, additional therapeutic measures which aim at halting, attenuating, or reversing the remodelling effects of the SNS and RAAS on the heart and blood vessels have been developed within the last thirty years for the management of HF patients. Therapeutic agents now used in addition to the standard therapy outlined above include angiotensin conversion enzyme inhibitors (ACEIs), vaso-dilators, calcium ion channel blockers, calcium ion mobilisation and utilisation modifiers and  $\beta$ -blockers.

Angiotensin conversion enzyme inhibitors prevent the conversion of angiotensin I to angiotensin II, inhibit the production of aldosterone and hence indirectly augment the effects of vasodilators if they are used together. The combination of ACEIs, vasodialtors, furosemine, an inotropic drug or inodilator, reduces the rate of HF deterioration of HF patients substantially (by up to 35%), engenders a better quality of life for both human and animal HF patients and reduces mortalities from HF by as much as 30 percent (Ettinger, et

al., 1994; Hamlin, et al., 1994; Bulmer and Sisson 2005). The most popular ACEI used in the management of HF in small animals is enalapril. Enalapril (Enacard®) has been shown to be very effective in the management of CHF even in Doberman pinchers suffering from DCM. Like other ACE inhibitors, it attenuates or even reverses some sub-cellular changes in the heart of dogs suffering from congestive HF. Other ACEIs like captopril, lisinapril, benazopril and ramipril have not been so widely used in animals. Generally, ACEIs are now considered to be useful in the management of CHF in its early stages and in cases that have become refractory to the standard therapy in both humans and animals. Apart from inhibiting the conversion of angiotensin I to angiotensin II, ACEIs lower the heart rate, control arrhythmias and alter baroreceptor sensitivity to hypotension (Ettinger, et al., 1994a; Bulmer and Sisson, 2005). They contribute very little, if at-all, to pre-renal azotaemia when used in combinations with glycosides and diuretics and therefore need not be withdrawn or modified dose-wise in such a cock-tail if the patient develops azotaemia (Ettinger et al., 1994b; Fox, 1994). Angiotensin conversion enzyme inhibitors are expected to reduce the release of aldosterone as a direct consequence of the reduction in the production of its secretagogue angiotensin II. However, it has been found that in spite of using ACEIs with diuretics and cardiac glycosides in the therapy for HF, some patients still develop high blood levels of aldosterone and suffer the consequences there-from. This has been attributed to the aldosterone escape phenomenon in which some angiotensin I evade the ACE inhibitors and get converted to angiotensin II probably in body tissues other than the lungs. The angiotensin II so produced subsequently activates the synthesis and release of aldosterone from the adrenal cortices (Bulmar and Sisson, 2005; Erling and Mazzaferro, 2008) with subsequent rebound of sodium and water retention and refraction to ACEIS. Such cases are treated with the addition

of spironolactone (aldactone®/spironolactone®) which is a competitive aldosterone receptor antagonist at a dose of 1-2 mg/kg bwt orally twice daily to the therapy. When used in such circumstances, spironolactone acts mainly to antagonise the vaso constrictive effect of aldosterone rather than as a diuretic. In addition, spironolactone directly suppresses the formation and deposition of fibrous and connective tissue in the interstitium of the failing heart. It therefore assists in attenuating the re-modelling changes in the heart associated with the development of HF. Other potassium sparing diuretics like eplerenone and triamterene may also have some anti-aldosterone and anti-remodelling effects (Bulman and Sisson, 2005).

Arterial and venous dilators reduce peripheral resistance and therefore increase peripheral capacitance. They reduce venous return to the heart, pre-load, forward impedance, and the left ventricular end-diastolic pressure but increase forward blood flow. These effects translate into less work by, less stress on, reduced oxygen demand and consumption by the ailing heart. There are thus an increased cardiac output, improved tissue perfusion and enhanced response to therapy. Of the large number of vaso-dilators available (Table 3), only hydralzine, prazosin and glycerine trinitrite (nitroglycerin pastes or creams) are commonly used in small animal practice. They should however, be used with care and under constant monitoring of the patient in order to avoid the development of life-threatening hypotension particularly if they are primarily arterial dilators and if they are administered in conjunction with diuretics. The combination of vasodilators with diuretics like furosemide can lower left ventricular end-diastolic pressure sufficiently to reduce mitral valve regurgitation and pulmonary overload by fifty percent (50%) in severe MVI within 24 to 36 hours of instituting such therapy (McIntosh, 1981; Bulmer and Sisson, 2005). This can improve a DCM or a MMVD patient's heart failure classification substantially within 48 hours (Atwell, 1979). A

recent drug, pimobendan (Vetmedin®) which has both a vaso- (arterial and venous) dilatory and inotropic effects (inodilator) has been used in dogs and found to be very effective in the management of congestive HF associated with DCM in dogs (Lompard, et al., 2006; Wolley, et al., 2007). Licensed for use in the management of congestive HF in dogs in the USA in 2005, pimobendan is claimed to be capable of reverting the remodelling processes that had occurred in HF and to increase survival times from an average of 9 months to 18 months (i.e. by up-to one hundred percent) from the time of diagnosis or institution of therapy over the survival times associated with the standard therapy (Anon, 2005; Gordon et al., 2006).

The catecholamines play an important role in the pathogenesis of HF through their direct effects on the cardio-vascular system, remodelling in cardiomyocytes and activation of the RAAS (Autran de Morias and Schwartz, 2005). They also cause a concentration dependent depression in the viability of cardiomyocytes resulting in increased apoptosis followed by inter-cellular fibrosis and collagen deposition. The RAAS which is later activated by the SNS actually tends to return to normal if the blood pressure is normalised. On the contrary, SNS remains activated and elevated in HF. This explains why it is the blood levels of nor-adrenaline rather than any other endogenous hormone like angiotensin II e.t.c. that correlates with both clinical deterioration and mortality rates of HF patients in humans. Therefore the early modulation of the SNS in HF with  $\beta$ -adrenergic blockers like atenolol, propranolol, carvedilol or satolol tend to be beneficial. These drugs lower peripheral vascular resistance, increase peripheral and systemic capacitance, improve forward flow and therefore cause improvement in cardiac function, particularly cardiac output, even though they tend to lower heart rates.

The calcium antagonist diltiazem tends to normalise calcium trans-membrane transport and the intracellular metabolism of calcium so

that cardiac function improves in DCM and MVI. Part of the therapeutic benefits derived from pimobendan (Vetmedin®) is also due to its ability to reduce intra-cellular calcium ion demand, enhance calcium ion metabolism, minimize oxygen demand but maximize its utilization by cardiomyocytes for a given level of function (Bulmer and Sisson, 2005).

Limited clinical trials with calcium channel blockers like amlodipine and nifedipine indicate that they may be useful in the management of HF in Small Animals out-patients because of their long duration of action (4-7 days) at a dose of 0.05mg/kg body weight orally (Bulmer and Sisson, 2005). When used in combination with diuretics, sympathomimetics like amrinone or milrinone, calcium channel blockers appear to improve the clinical states and delay deterioration of human HF patients but do not seem to prolong life or reduce mortality. They may in fact increase mortality by as much as 28- 53 percent (Bulmer and Sisson, 2005). This suggests that they should be used with great caution and under very close observation in HF patients. More clinical work needs to be carried out in this and other areas in order to determine if calcium channel blockers can be useful in the management of HF in animals.

Depending on the severity and prognostic outlook of phase II or III chronic HF in dogs and cats, the drugs discussed above may be used alone or in various combinations with diuretics, oxygen supplementation and inotropes depending on the initiating cause of the HF. Vaso-dilators, ACEIs, inotropes are specifically indicated in systolic or low output failure such as DCM, MVI for so long as such systolic failure is not due to valvular incompetence (Bulmer and Sisson, 2005).

Newer pharmaceutical preparations are currently being studied for their effectiveness in the management of HF in man and animals. These include angiotensin II receptor antagonists like losartan which could be useful in cases associated with aldosterone escape phenomenon, other calcium sensitisers,

endothelium antagonists like bosentan and drugs that promote atrial natriuretic hormone production like ecdotril. Stem cell transplantation is also being investigated for use in the treatment of HF in man and animals (Jiang-Yong et al., 2002; Bulmer and Sisson, 2005). Recently there were announcements of discoveries of techniques for the production of body organs synthetically. These all point to new scientific advances that may pave the way for novel treatments for such eventual terminal ailments like HF and neoplasia.

The mechanisms that sustain the activated SNS, the RAAS and tissue responsiveness to them even after the blood volume, blood pressure and cardio-vascular functions have returned to normal are, at present, only poorly understood. Such information, when available, may provide additional focus for further therapeutic developments in the management of HF in man and animals. Already, it has been shown that several drugs notably the ACE inhibitors attenuate several changes in the failing heart through a variety of mechanisms. Presently, it is impossible to prevent the eventual fatality from HF in both man and animals. But it has recently been shown that it is possible to prolong the lives of such animals to the extent that affected patients live long enough to die of other causes in the intervening period. As more pharmaceutical agents are discovered and tested, it is hoped that drugs that are capable of completely reversing the sub-cellular remodelling seen in HF will be found. Then it may be possible to provide a cure for the failing heart in both man and animals

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