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HEART FAILURE - MANAGEMENT OF CONGESTION:
USE OF ACE-INHIBITORS, DIURETICS, AND SALT RESTRICTION

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The most important signs of heart failure, such as dyspnea (due to pulmonary edema or pleural effusion) and ascites, are directly attributable to sodium and fluid retention resulting from activation of the renin-angiotensin-aldosterone system (RAAS). Management of the signs of congestive heart failure (CHF) has relied upon the use of natiuretic diuretics (furosemide), restriction of dietary sodium, and more recently angiotensin converting-enzyme inhibitors (ACE-I) which, by blocking aldosterone production, combat sodium retention and congestion. In addition, as vasodilators, ACE-I unload the heart, improving cardiac output and exercise, normalize electrolyte aberrations, and blunt the pathological cardiovascular remodeling produced by angiotensin II and aldosterone.

While off-loading therapy with the aforementioned drug groups can be life-saving, their use can be associated with adverse side-effects. Most notable of these are hypotension, azotemia, renal failure, and arrhythmias. Certain complications are more apt to occur when combinations of drugs are used. Because of the potential for such side effects, these drugs are best employed in specific sequence and combinations. The following discussion relates to their use in the management of chronic heart failure.

ANGIOTENSIN CONVERTING-ENZYME INHIBITORS

In landmark veterinary studies of enalapril in NYHA phase III and IV heart disease (moderate to severe heart failure), due to mitral regurgitation (MR) and dilated cardiomyopathy (DCM), enalapril improved survival by >100% as well as reducing pulmonary edema and, improving quality of life scores. Exercise capacity is also improved in dogs with experimental mitral insufficiency. Benazepril has likewise been shown to improve survival. ACE-I have proven to provide additional benefits in human patients by blocking pathological remodeling, presumably slowing progression of heart disease and by normalizing serum electrolyte concentrations. Today, ACE-I represent the cornerstone in the chronic management of CHF. They are indicated in virtually all cases of systolic heart failure in which they are tolerated.

There was early concern regarding the renal safety of these compounds and all ACE-I, which have enjoyed extensive clinical use, have been associated with renal dysfunction, usually temporary. There has been speculation that, at very high doses (180x the clinical dosage), ACE-I have direct nephrotoxic effects but it is generally felt that the major impact of ACE-I on the kidney, with clinically relevant dosages, is through production of hypotension, thereby reducing the renal perfusion pressure and resulting in worsening of azotemia. To date, veterinary
Clinicians have had experience with enalapril, captopril, benazepril, and lisinopril. Of these, only enalapril has been extensively studied and is licensed for use in management of heart failure in the United States, though benazepril has been marketed in Europe and Canada. The active metabolite of benazepril is reportedly excreted both in the bile and in the urine so that lower serum concentrations are evident in experimental renal disease. The clinical relevance of this is unclear. Over 10 years of veterinary clinical experience with ACE-I (mainly captopril and enalapril) have taught us that their impact on kidney function is minimal even in the face of severe heart failure. When azotemia is observed, ACE-I are almost always being used in conjunction with diuretics and sodium restriction with resultant hypotension. Typically, diuretic cessation or reduction in the dosage results in the reversal of azotemia.

In studies of enalapril in NYHA phase III and IV heart disease (moderate to severe heart failure), due to MR and DCM, there was actually a lower incidence of azotemia in the enalapril-treated group than the placebo-treated group. Furthermore, in an ongoing study of enalapril’s role in the delay or prevention of heart failure due to naturally-occurring MR, interim analysis showed that enalapril at the standard dosage of 0.5 mg/kg daily had no effect on serum creatinine concentrations, as compared to placebo.

In fact, evidence is building to prove benefit when ACE-I are administered chronically to both human and veterinary patients with naturally-occurring and experimental renal failure. Mechanisms for this improvement are postulated to be the antihypertensive effect, reduction of angiotensin II-induced mesangial cell proliferation, and renal vasodilatory effects of ACE-I, the latter related to a fall in renal filtration pressure and proteinuria. Enalapril has recently been shown to reduce urine protein loss and reduce blood pressure in naturally-occurring canine glomerulonephritis. Likewise, benazepril reduced azotemia and proteinuria in a short-term study of experimental and naturally-occurring renal insufficiency in cats and lowered BUN and creatinine concentrations and blood pressure in cats with polycystic kidney disease.

As mentioned above, ACE-I have the potential to produce symptomatic hypotension. This is due to the mixed vasodilatory effect of this group of drugs and is typically observed when ACE-I are used in conjunction with other off-loading therapies, such as vasodilators, diuretics, and sodium restriction. Hypotension is reversed by altering drug therapies but may be problematic in producing azotemia, inappetance, weakness, lassitude, and precipitating digitalis intoxication by reducing renal elimination.

SODIUM RESTRICTION

The salt avidity that results from aldosterone secretion in heart failure has been well documented. Sodium restriction contributes to signs of congestion (pulmonary edema, ascites, pleural effusion) and hence reduction in salt intake is logical. There is little data on clinical outcomes with such strategy but stringent salt restriction with diuresis has been shown to reduce total body sodium stores while, paradoxically, blunting acute furosemide-induced diuresis. Roudebush demonstrated that neither moderate nor severe salt restriction alone caused azotemia in aged, normal dogs, but when furosemide (3.2 mg/kg b.i.d.) was coupled with severe (but not moderate) salt restriction, serum creatinine rose by 63% - more than twice as much as in dogs receiving a diet with a standard sodium content. Furthermore, both moderate and severe salt restriction activated the renin-angiotensin-aldosterone system (RAAS) and when furosemide was added to the regimen, there was nearly a 6000-fold increase in serum aldosterone concentration with severe salt restriction. Finally, it is well established that salt restriction increases the
likelihood of azotemia with ACE-I therapy.\textsuperscript{10}

One can conclude that sodium restriction, while logical and likely useful in reducing total body sodium concentration and diuretic requirements, is not without a toll. This toll represents the tendency to increase azotemia with concurrent diuretic and ACE-I therapy and to activate the RAAS. Use of moderate salt restriction (e.g., a diet designed for renal patients with .22\% sodium by dry weight) early in heart failure is advisable, with severe salt restriction (.10\% sodium by dry weight) being reserved for patients refractory to therapy. Concurrent diuresis should be avoided as long as possible and ACE-I should accompany sodium restriction and diuretic therapy in heart failure.

\textbf{DIURETICS}

The most widely used diuretic is furosemide, a loop diuretic. It is potent and, while life-saving, it has the potential to produce azotemia, hypotension, and electrolyte disturbances, to lower cardiac output and to activate the RAAS.\textsuperscript{23,24} Fatal arrhythmias have been associated with “non-potassium sparing diuretics”.\textsuperscript{25} Furosemide is not primarily nephrotoxic, though it can potentiate other nephrotoxic drugs. It produces prerenal azotemia by dehydration and hypotension and has a synergistic effect in diminishing renal function when used with either ACE-I or sodium restriction.\textsuperscript{10,23,24}

Furosemide is the drug of choice for life-threatening pulmonary edema but should otherwise be used only as needed to control signs of congestion. In other words, because it activates the RAAS, lowers blood pressure and cardiac output, causes azotemia and electrolyte disturbances, and potentiates adverse effects of other cardiac therapies, it should not be used as a monotherapy (i.e., with the exception of emergency therapy, furosemide therapy should always be accompanied by an ACE-I) and should be used at the lowest dosage compatible with good quality of life. If azotemia develops in a patient receiving polypharmacy, the first change should be the decrement or cessation of furosemide.

The aldosterone antagonist, spironolactone, has received renewed interest with a report that life expectancy was prolonged in humans with heart failure when spironolactone was administered concurrently with conventional therapy in NYHA phase IV patients.\textsuperscript{26} Because spironolactone is a weak diuretic, particularly at the modest dosage used in this study, the investigators concluded that benefits were due to blunting the adverse effects of aldosterone. This drug might logically be used early in heart failure for this reason, but there is not data for early or pre-heart failure states. It is meant to compensate for temporary or incomplete suppression of aldosterone secretion by ACE-I and should be used concurrently with ACE-I.

\textbf{CONCLUSION}

Of the 3 therapeutic strategies discussed, loop-diuretic therapy has the greatest potential for adverse side-effects (hypotension, azotemia, activation of RAAS, electrolyte disturbances and fatal arrhythmias). Therefore, except in emergencies, furosemide should not be used as monotherapy and should be used at the lowest dosage possible which prevents signs of CHF. Salt restriction has similar, but lesser effects on RAAS activation, and potentiates diuretic- and ACE-I-induced tendencies toward azotemia.\textsuperscript{3,4} Therefore, moderate, rather than severe salt restriction, is indicated until signs of heart failure become refractory. Of the drugs under discussion, only ACE-I have been shown to benefit heart failure while blunting other pathophysiological processes (RAAS activation, electrolyte abnormalities, aldosterone- and
angiotension II-induced cardiac remodeling, and renal dysfunction). Therefore, if either azotemia or hypotension is noted in a patient being managed for heart failure, the diuretic should first be discontinued or the dosage reduced, being reinstituted as necessary. Reduction or cessation of ACE-I is employed only if altering the diuretic dosage is ineffectual. Though ACE-I are generally safe, BUN and creatinine, as well as serum potassium concentration and systemic blood pressure should be monitored periodically, particularly if sodium restriction and/or diuretic therapy are utilized concurrently. Finally, when any of these agents are utilized, either alone or in combination, if caution is exercised and hypotension avoided, there is little risk of significant renal impairment.

References
Available upon request.

Figure 1. Overview of management of heart failure.