Current Concepts in Vasodilator Therapy for Advanced or Refractory Congestive Heart Failure

Michael S. Miller, Michael R. O'Grady and Francis W. K. Smith Jr.

Abstract

The use of vasodilators to assist in the management of advanced heart failure has gained widespread acceptance in human cardiology. The early experience with these same drugs in the management of heart failure in domestic animals has similarly been encouraging.

Vasodilators function to favorably alter preload and afterload in the heart failure setting. Venodilators can resolve pulmonary edema by reducing an elevated left heart preload. Arterial vasodilators can increase stroke volume, reduce an elevated preload, and blunt or abolish the stimulation of the harmful compensatory measures that are induced in the presence of heart failure. Both classes require careful monitoring to ensure that marked hypotension does not occur.

Vasodilator therapy can significantly complement other traditional modalities of drug therapy in cases of advanced heart failure.

Résumé

L'utilisation de vasodilatateurs dans le traitement de l'insuffisance cardiaque sévère a démontré son efficacité en cardiologie humaine. Chez les animaux domestiques, les résultats de l'utilisation de ces médicaments sont tout aussi encourageants.

Les effets thérapeutiques des vasodilatateurs résultent d'altérations de la pré-charge et de la post-charge dans le cadre de l'insuffisance cardiaque congestive. Les dilatateurs veineux peuvent éliminer l'oedème pulmonaire en diminuant la pré-charge du ventricule gauche. Les dilatateurs artériels pour leur part peuvent augmenter le volume d'éjection, diminuer une pré-charge élevée et même atténuer ou éliminer la stimulation de mécanismes de compensation indésirables qui sont activés par l'insuffisance cardiaque même. L'administration de ces médicaments nécessite un suivi attentif pour éviter l'hypotension sévère.

L'utilisation des vasodilatateurs peut complémenter significativement les autres modes de thérapie conventionnelle dans les cas d'insuffisance cardiaque congestive sévère.

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Introduction

Vasodilator therapy has been clearly shown to play a beneficial adjunctive role in the management of acute and chronic heart failure in man (1-5). Although no similar large group placebo-controlled studies are available in veterinary medicine, very small-group clinical impressions would suggest a similar beneficial role in the management of heart failure in companion animals (6,7).

We will begin this review with a brief synopsis of the factors which influence myocardial performance, since vasodilator therapy functions to alter several of these factors. The performance of the heart is usually determined by measuring the cardiac output (volume of blood ejected per minute) or stroke volume (volume of blood ejected per contraction). Consequently, heart failure may be considered to exist when the cardiac output is insufficient to meet the metabolic needs of the tissues (8). Furthermore, congestive heart failure is said to exist when pulmonary venous congestion occurs in addition to the state of reduced cardiac output. A number of parameters have been shown to influence the heart in its attempt to meet the metabolic demands of the peripheral vascular beds. These factors are known as the determinants of myocardial performance and include preload, afterload, contractility, heart rate, distensibility, and synergy of contraction (1,2,4-6,8-11). It is beyond the scope of this review to discuss these parameters in detail; nevertheless, an overview of the significance of each of these and how they alter myocardial performance is necessary to the understanding of the beneficial effect of vasodilators on the failing heart.

Preload may be defined as the amount of myocardial fiber stretch just prior to the onset of contraction (1,2,5,6,8-10,12,13). Therefore, preload refers to the volume of blood present in the ventricle just prior to the onset of contraction. Preload is usually measured as the end diastolic volume or end diastolic pressure of the left ventricle. As preload increases, stroke volume increases; on the other hand, conditions that result in a fall in preload also result in a reduction in stroke volume (8-10). This relationship between preload and stroke volume is described by the Frank-Starling Law and function curve (Figure 1) (8-10). It is worthwhile to briefly review the function curves for both the normal and failing heart. Note that in the normal heart, as preload increases, stroke volume rises sharply; however, in the failing heart, the curve is significantly depressed and shifted to the right such that marked increases in preload produce only a modest improvement in stroke volume. Also note that the curve for a failing heart has an initial steeper phase and a later plateau phase. The significance of these phases to the failing heart lies in the fact that large changes in preload cause only minor changes in stroke volume along the plateau portion of the curve. The Frank-Starling curves also depict the relationship between increases in left ventricular preload and the development of pulmonary edema (12,13). As ventricular filling pressures rise, pulmonary capillary

Cardiopet, Inc., 25 Lumber Road, Roslyn, New York 11576-2105 (Miller, Smith) and Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Guelph, Ontario N1G 2W1 (O'Grady).

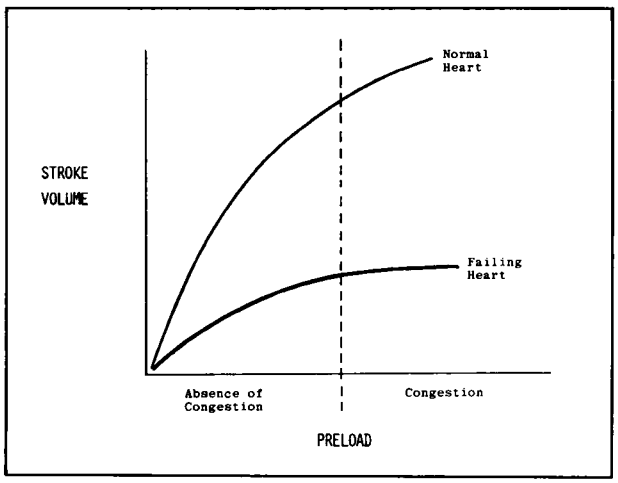

Figure 1. Two Frank-Starling function curves are represented; one for a normal heart and one for a failing heart. The dotted line represents a hypothetical level of preload greater than which will result in pulmonary edema (to the right of the dotted line).

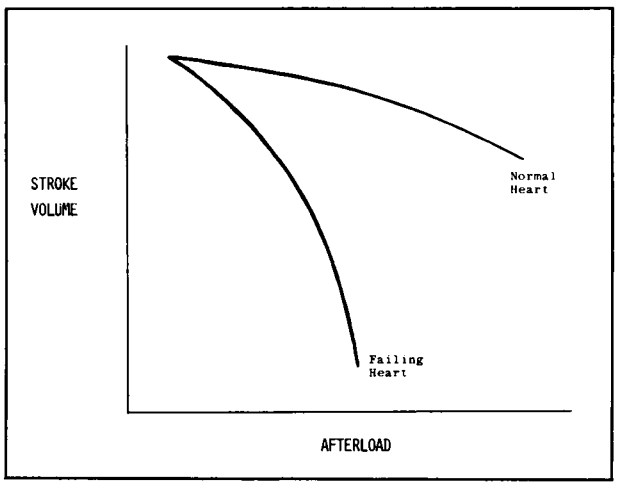

Figure 2. The inverse relationship between stroke volume and afterload is represented for a model of a failing heart and a normal heart.

hydrostatic pressures also rise resulting eventually in pulmonary edema. Therefore, when reviewing the function curve for a failing heart, one observes that a relatively large reduction in preload results in moving along the plateau portion of the curve (to the left) with a minimal reduction in stroke volume. However, significant reductions in left ventricular filling pressure and subsequently pulmonary capillary hydrostatic pressure occur, resulting in a resolution of pulmonary edema.

Afterload is a very difficult term to define because it is primarily conceptual. It is frequently thought of as the resistance to left ventricular ejection and is dependent on a number of factors including arterial vasomotor tone and left ventricular volume (6,9,10). The relationship between stroke volume and afterload has been diagrammatically depicted in Figure 2 (5). Note that for both the normal heart and the failing heart, as afterload increases, stroke volume falls and vice versa. Note further, that the magnitude of the change in stroke volume for the same increment of change in afterload differs markedly for the normal and failing heart. Consequently, large changes in stroke volume occur with modest changes in afterload in the setting of a failing heart. Afterload is reduced when the arterial vasomotor tone is reduced or when ventricular volume is reduced (6,9,10). Conversely, afterload is increased when the arterial vasomotor tone is enhanced or when ventricular volume is increased.

Contractility refers to the intrinsic ability of the myocardial fibers to shorten (9,10). Increases in contractility result in more complete ventricular emptying during systole; consequently stroke volume increases. Although a number of factors may increase contractility, two important factors are a reduction in afterload and the presence of drugs or metabolites, i.e. catecholamines, which increase the availability of intracytoplasmic Ca^{++} to the contractile apparatus (10).

Heart rate is another important determinant of myocardial performance; increases in heart rate result in increased cardiac output (10). However, this beneficial effect becomes self-limiting at high rates because ventricular filling and coronary perfusion may be severely compromised (10,11). Furthermore, at higher heart rates, the myocardial energy requirements may be excessive resulting in inefficient anaerobic function (9,10). This may result in a reduction of contractility and promote arrhythmogenesis.

Distensibility refers to the ability of the heart to fill during diastole (8,10,14). In this respect, it is related to preload in that disorders of distensibility are characterized by inadequate ventricular filling. Thus, we are here referring to a specific etiology for reduced preload and subsequently a reduction in cardiac output. Disorders of distensibility include infiltrative myocardial disorders, endocardial disorders with fibrosis, and pericardial disease, all of which restrict the ability of the ventricle to fill in diastole (8,14).

Finally, disorders characterized by *dyssynergy of contraction* alter myocardial performance (11,12). In this category, we refer to those disorders that are NOT characterized by the normal sequence of atrial and ventricular activation. The normal sequence of chamber activation results in a harmonious and efficient ventricular ejection of blood; in the dyssynergic group of disorders we refer to abnormalities which result in asynchronous, haphazard, or even chaotic ventricular activation resulting in either a markedly reduced or negligible stroke volume. These disorders usually result from the development of arrhythmias.

Integration of the Determinants of Myocardial Performance

Let us now examine how several of these determinants of myocardial performance influence cardiac output in disease states. In a disorder characterized by a profoundly weakened heart muscle, such as dilated cardiomyopathy, a number of changes will occur in the determinants of myocardial performance. Heart failure may be characterized as a state of reduced cardiac output

as previously stated. The following usually occur as a result of this abnormality:

a) An increase occurs in the total circulating blood volume, particularly in the cardio-pulmonary circuit. This enhanced circulating fluid volume results from activation of the renin-angiotensin-aldosterone system and arginine vasopressin (8,15). This is beneficial because it results in an increase in preload, in an attempt to maximize cardiac output. Remembering how the Frank-Starling curve is shifted downward and to the right for the failing heart, this increase in preload may offer only mild increases in cardiac output, while it may result in very markedly elevated ventricular filling pressures and subsequently pulmonary edema (8,12,13). Ventricular dilation will also occur as a result of the increased fluid in the cardio-pulmonary circuit; this increased ventricular volume increases afterload (6,9,10).
b) An increase in afterload results due to an increase in arterial vasomotor tone and ventricular dilation (as just discussed). The increase in arterial resistance (due to an enhancement of arterial vasomotor tone) occurs due to activation of the sympathetic nervous system, renin-angiotensin-aldosterone system and arginine vasopressin, all occurring in response to the fall in cardiac output (6,8,15). This increase in arterial resistance maintains blood pressure to vital vascular beds (coronary and cerebral) (8); however, the increase in afterload results in a further deterioration in cardiac output (Figure 2) (5).
c) In most forms of heart failure, the inherent myocardial contractility is reduced (8). As afterload increases, further reductions in contractility occur (5).
d) Heart rate usually rises in heart failure in an attempt to augment cardiac output (7,8). However, unless an arrhythmia also occurs, this degree of increase in heart rate is usually not harmful.
e) Many forms of heart failure are characterized by only mild changes in distensibility.
f) As stroke volume and consequently coronary perfusion fall and as the myocardial energy requirement increases, arrhythmias may develop (11,12). Usually, individuals with moderate reductions in cardiac output are asymptomatic until the development of dysrhythmias and the resultant dyssynergy of contraction occur (11,12). Cardiac output subsequently falls precipitously and severe signs of heart failure are manifest.

In a disorder characterized by a hypertrophic myocardium as typified in feline hypertrophic cardiomyopathy, a number of changes also occur in the determinants of myocardial performance.

a) The excessively thickened (hypertrophic) myocardial walls severely reduce left ventricular distensibility (8,10,14). Thus left ventricular preload is reduced; consequently stroke volume is reduced. The left atrial preload becomes elevated, because of the inability to fill the non-distensible ventricle. Pulmonary venous congestion and pulmonary edema may result.
b) As cardiac output falls, afterload becomes elevated due to the enhanced arterial vasomotor tone, as described in the previous example.
c) Although one might expect contractility to be normal or enhanced due to the increase in myocardial mass, this "muscle-bound" heart tends to develop at least mild reductions in contractility (8,16).
d) Heart rate tends to be moderately elevated, as in the first case discussed.
e) This disorder is a classic example of reduced distensibility with subsequent reductions in cardiac output (8,10,14).
f) Dysrhythmias may develop as a result of the reductions in coronary perfusion and myocardial hypertrophy (11,12,17).

Rationale for Vasodilator Therapy

Therapeutic strategies currently used to treat failure include positive inotropic agents, diuretics, restriction of sodium intake, restriction of physical activity, and mechanical removal of pleural and abdominal effusions (5–7,14).

However, abundant evidence indicates that measures that reduce preload by venodilation and reduce afterload by reducing arterial vasomotor tone via arterial vasodilation can improve cardiovascular hemodynamics (1–7,14).

As the previous two examples illustrate, many of the determinants of myocardial performance become altered in cardiovascular disease states. Furthermore, many of these alterations contribute markedly to the signs of heart failure, as well as possibly enhancing the progression of the underlying disorder. Vasodilator therapy can directly modify preload and afterload, and indirectly modify contractility, heart rate, distensibility, and synergy of contraction (1–7,14).

Venodilators function to dilate venous capacitance vessels. In that the venous limb of the circulation holds approximately 80% of the circulating blood volume, even a small amount of venodilation will result in "trapping" a large volume of blood in the venous compartment (1–7,14). Consequently, venodilation results in shifting blood from the cardiopulmonary circuit into the peripheral venous system. Therefore the results of venodilation include (1–7,14):

a) A reduction in capillary hydrostatic pressure with resolution of edema formation, especially pulmonary edema, and effusions.
b) A reduction in ventricular end-diastolic volume and pressure. This assists cardiac performance via a reduction in afterload.
c) A reduction of venous return which reduces preload with a resultant fall in stroke volume (Frank-Starling relationship).

Let us recall that the failing heart Frank-Starling curve has a plateau portion (Figure 1). Marked reductions in preload (moving to the left along the plateau portion of the curve) cause relatively mild reductions in stroke volume. Therefore, in severe heart failure, venodilator therapy may resolve severe pulmonary edema with only mild reductions in cardiac output.

Note, however, that excessive reductions in preload can markedly reduce stroke volume resulting in hypotension (Figure 1).

Vasodilators with the capacity to induce arterial dilation by blocking the increases in arterial vasomotor tone can markedly reduce afterload in the heart failure setting (1-7,14). This can be beneficial by increasing contractility and stroke volume. Recall how the response to afterload reduction in the failing heart is significantly greater than that of the normal heart (Figure 2). The improved cardiac output may result in (1-7,14):

a) A retardation or abolition of the compensatory measures which induced the enhanced afterload and fluid retention.
b) A reduction in ventricular volume (due to the more complete ventricular emptying at end systole) further reducing afterload and also reducing preload.
c) A resolution of pulmonary edema by reducing preload.
d) An increase in coronary perfusion as cardiac output increases with a resolution of dysrhythmias.

The potential adverse effects of arterial vasodilation include a marked reduction in blood pressure leading to hypotension. However, because blood pressure = (cardiac output) × (arterial resistance) (14), the blood pressure tends to remain normal due to the rise in cardiac output induced by afterload reduction (reduced arterial resistance) (8).

Detection of Abnormalities in Preload and Afterload

Given the potential for vasodilator therapy to provide significant hemodynamic benefit through preload and afterload reduction, it next behooves us to examine the readily available means to detect abnormalities of preload and afterload in cardiovascular disease states.

To detect an elevation in preload, a careful examination of the jugular veins can be helpful. The presence of distention, pulsations, or the induction of jugular venous distention with moderate pressure placed over the region of the liver (a positive hepatojugular reflux response) indicate the presence of an elevated right atrial pressure, which is usually present in congestive heart failure (18). Other findings that may be detected on physical examination to suggest an elevated preload include pleural effusion or ascites (7). An elevated central venous pressure measurement will document the elevated preload (19). Thoracic radiography demonstrating the presence of pulmonary venous distention with or without pulmonary edema is another very useful routine test to demonstrate an elevated preload (7,20). Other tests not routinely available to the practitioner to detect an elevation in preload include pulmonary capillary wedge pressure (PCWP) measurement (19) and echocardiographic left ventricular internal dimension at end-diastole (21). The PCWP is obtained by measuring the hydrostatic pressure via a balloon-tipped catheter advanced and wedged into a branch of the main pulmonary artery.

The detection of abnormalities of afterload in the clinical setting is very difficult. There are no physical examination findings or routine laboratory aids which can indicate the level of afterload in a particular individual. Routine radiographs of the chest may suggest an elevation in the ventricular chamber dimensions, however, an enlargement of the cardiac silhouette on radiography may occur a result of an increase in wall thickness with no enlargement of ventricular chamber dimensions. One can nevertheless infer changes in afterload by deducing the changes that occur in a principal determinant of afterload, arterial resistance. Given the relationship between arterial resistance and blood pressure, namely (14):

$$\text{arterial resistance} = \frac{\text{blood pressure}}{\text{cardiac output}}$$

as cardiac output falls in heart failure, and sympathetic tone rises to maintain blood pressure, arterial resistance must increase. A number of abnormalities may be present in the history, physical examination, and laboratory aids to suggest a fall in cardiac output. These include: historical findings of reduced exercise tolerance, weakness, or syncope; physical examination findings of weakness, slow capillary refill time, pale mucous membranes, and cool extremities, and laboratory findings of prerenal azotemia due to reduced renal flood flow (7). Therefore, when cardiac output falls, we infer a rise in arterial resistance and consequently in afterload.

Classification of Vasodilators

The available vasodilators differ in mechanism, site of action, and method of administration. A recent classification (6) grouped vasodilators by their mechanism of action: 1) direct acting vasodilators, including the venodilator nitrates and arterial dilator hydralazine; 2) alpha-adrenoreceptor blockers such as prazosin; and 3) angiotensin converting enzyme inhibitors such as captopril and enalapril. A more useful clinical classification groups vasodilators according to their site of action into arterial and venous dilators (Table 1) (22,23). It must be emphasized that although a vasodilator may have a primary site of action, the hemodynamic changes induced may result in secondary effects on both preload and afterload.

Indications for Vasodilator Therapy

Venodilator therapy should be considered in cases with objective evidence of an elevation in preload. The ideal situation of venodilator therapy would be the patient presented with fulminant pulmonary edema (5,6). Rapid reduction of the fluid overload by reducing circulating volume (diuretic therapy) and by reducing capillary hydrostatic pressure (venodilator therapy) is indicated. This will reduce pulmonary edema and enhance oxygenation. By improving respiratory function, this will provide time to institute measures to augment stroke volume, thus counteracting the cause of the pulmonary edema. Therefore, venodilator therapy is particularly useful to reduce preload on an acute, short-term basis. One should strive to maintain a reduced preload state by enhancing stroke volume, which can be accomplished by the use of arteriolar dilator therapy and positive inotropic therapy. For those individuals that fail to resolve their pulmonary

TABLE 1
Vasodilators Commonly Used in Veterinary Medicine

Product	Vasodilator Site of Action	Mode of Administration	How Supplied	Dosage	Other Comments
Nitroglycerin ointment 2%	exclusively venous dilator	topical-apply to hairless areas such as inside of pinna of ear, thorax, or abdomen	ointment — 2% Nitrol® (Kreamers-Urban) Nitro-Bid® (Marion)	1/8 - 1 inch cutaneously q6-8h (dogs); 1/8-1/4 inch q6-8h (cats)	— helpful in treatment of severe pulmonary edema, pleural effusion, or ascites — usually used in hospitals only, due to potential for client misuse — must wear gloves — syncope by hypotension with overdose
Prazosin	arterial and venous	P.O.	1,2, 3mg capsules Mini press (Pfizer)	0.5-2.0 mg q8-12h (dogs); dosage not established in cats	— action may not be as potent or as consistent as hydralazine — syncope by hypotension
Hydralazine	arterial dilator	P.O.	10,25,50,100mg tablets; 1mL ampules Apresoline® (Ciba)	0.5-2.0 mg/kg q12h (dogs); 2.5 mg P.O. q12h (cats)	— rapid onset action, sustained increase in cardiac output — reduces regurgitation in mitral insufficiency
Nitroglycerin Hydralazine (together)	venous/arterial	topical/P.O.	as above	as above	— combination effect increasing cardiac output and controlling systemic congestion
Captopril	arterial and venous	P.O.	12.5,25,50 mg tablets Capoten® (Squibb)	0.5-2.0 mg/kg q8-12h (dogs); 1/8-1/4 of a 25 mg tablet q8-12h (cats)	— effective arterial and venous dilator — improves cardiac output as well as controls pulmonary edema and ascites — requires good renal function for excretion — hypotension may occur after first or second dose

P.O. = per os

edema with such measures to enhance stroke volume and diuretic therapy on a long-term basis, then adjunctive maintenance venodilator therapy may be necessary.

It should be emphasized that, if preload is already reduced (e.g. dehydration), a venodilator will cause a further reduction in cardiac output and signs of hypotension (5,6). Hypotension is more likely to occur when venodilator therapy is combined with diuretic therapy (5,23). Therefore, careful monitoring for evidence of an over reduction of preload is important.

Arterial dilator therapy should be considered in cases with evidence of an elevation in afterload in the heart failure setting. The typical case would be that of congestive heart failure due to dilated cardiomyopathy (6). Arterial dilator therapy may significantly augment traditional therapy (digitalis, diuretics, low sodium diet, and rest) by reducing arterial resistance and thereby increasing stroke volume (1-8,14,22,23). Experimental evidence has demonstrated that arterial dilator therapy will assist cases of chronic severe mitral valve insufficiency by promoting forward flow from the left ventricle and reducing regurgitant flow (6,14). This reduction in regurgitant flow retrograde across the mitral valve will tend to reduce the left atrial enlargement and secondary bronchial compression and coughing prevalent in the setting of severe mitral valve insufficiency in dogs. Cases of congenital heart disease with left to right shunts (e.g. ventricular septal defect, patent ductus arteriosus) may benefit from acute and chronic vasodilator therapy (5,14).

As with venodilators, arterial vasodilators may cause severe hypotension and collapse (6,14,23). In that arterial blood pressure is rarely monitored, the clinician must proceed cautiously with these agents and work closely with owners to detect early signs of hypotension.

Vasodilators Commonly Used in Veterinary Medicine

1. *Nitrates* (5,6,23,26):
   Primary effect: Direct acting venodilator; relaxation of the smooth muscle of peripheral vascular beds; pooling blood in veins results in reduced left atrial and left ventricular pressures and intracardiac volume.
   Hemodynamic effects: Reduces PCWP and right atrial pressures; pulmonary artery pressure and systemic vascular resistance may also decrease

somewhat. With low or normal preload, there will be a further reduction in stroke volume and cardiac output, and systemic arterial blood pressure may decrease. The nitrates can be used with arterial dilators. The dosage of concomitant diuretic therapy may need to be reduced to treat heart failure. Recent studies suggest that nitrates are also moderate arterial dilators, depending on the dosage and route of administration.

Indications: Severe pulmonary edema, pleural effusion, or ascites due to congestive heart failure, especially small breed dogs, refractory to therapy with diuretics alone.

How supplied: Topical 2% nitroglycerin ointment (Nitrol, Kreamers-Urban; Nitro-bid, Marion), and isosorbide dinitrate (Isordil, Ives) 10,20, and 30 mg scored tablets.

Dosage: Nitrol, Nitro-bid, in dogs and cats: 1/8 to 1/4 inch for small dogs and cats (a maximum of 1 inch for giant dogs) applied topically with gloves to the inside of the pinna of the ear, or shaved portions of the thorax or abdomen q6-8h; Isordil, in dogs: 0.5–2.0 mg/kg q8h, per os.

Side effects and limiting factors: Although the nitrates have not been critically studied in domestic animals with heart failure, they have been used clinically (especially nitroglycerin ointment) with success, in dogs and cats with heart failure. Hypotension is the most serious side effect. The short half life of the nitrates has been acceptable for long-term heart failure therapy. Clients should be warned to avoid exposure to the ointment by wearing gloves.

2. *Hydralazine* (23–26):

Primary effect: A direct-acting arterial dilator; causes direct relaxation of the smooth muscle of the peripheral vascular bed. Hydralazine is the only vasodilator that has been well studied clinically in veterinary medicine at the present time.

Site of action: Dilates arterioles either by elevating local concentrations of prostaglandin or by inhibiting calcium transport into the vascular smooth muscle cells.

Hemodynamic effects: A reduction in arterial resistance (afterload) resulting in an increase in cardiac output. There is a secondary reduction in left atrial and left ventricular volume (preload) and therefore pulmonary edema.

Indications: Acute and chronic congestive heart failure due to mitral regurgitation, congestive heart failure due to dilated cardiomyopathy, or congenital heart disease with left to right shunts.

How supplied: Hydralazine hydrochloride (Apresoline, Ciba), 10, 25, 50, and 100 mg tablets and 1 mL ampules.

Dosage:

A) Dogs: 0.5–2.0 mg/kg/po q12h. A detailed hydralazine titration protocol has been reported in the dog (26), but requires the measurements of mixed venous oxygen tension and arterial blood pressure which is prohibitive for most practitioners. Oral arterial vasodilator therapy can be safely used if individuals are started on a low dose (hydralazine 0.5 to 1.0 mg/kg (p.o. q12h) for 1 week, then increased to the maintenance dose of 1.0 — 2.0 mg/kg (p.o. q12h). Careful attention to signs of hypotension is required.

B) Cat: 2.5 mg per os q12h.

C) Intravenous hydralazine doses have not been established for the dog and cat.

Side effects and limiting factors: Hypotension, tachycardia (concurrent digoxin may be needed), anorexia, and vomiting (more common in cats). Hydralazine also stimulates the renin-angiotensin-aldosterone system. Elevated aldosterone levels develop after hydralazine administration in humans, which increases fluid retention and causes a worsening of pulmonary edema in some patients. Higher doses of diuretics may then be required (27).

3. *Prazosin* (6,14,23):

Primary effect: A postsynaptic alpha-receptor blocking agent that decreases vascular tone (both arterial and venous) and arterial resistance.

Site of action: A balanced effect on arteries and veins.

Hemodynamic effects: Reduces arterial resistance and pulmonary venous pressure which results in an increase in cardiac output and reduction in pulmonary edema. Heart rate usually remains unchanged. A marked hypotensive response may be seen after the first dose of prazosin in man, therefore therapy should probably be started cautiously in the dog.

Indications: The same as for nitroglycerin and hydralazine. This drug will provide combined afterload and preload reduction.

How supplied: Prazosin (Minipress, Pfizer) 1 mg, 2 mg, 3 mg capsule.

Dosage: 0.5–2.0 mg q12h per dog. Dosage is not established in the cat. A gradual increase in the dose to maintenance levels may reduce the incidence of hypotension, as described for hydralazine.

Side effects and limiting factors: A marked hypotensive response may be seen after the first dose in man. Sustained effectiveness of this drug to improve cardiac output and relieve congestion is not established in the dog. Urinary incontinence may develop.

4. *Captopril* (23,26,28):

Primary effect: An oral drug that acts as an angiotensin converting enzyme inhibitor thereby inhibiting the formation of angiotension II and aldosterone.

Site of action: A balanced effect on arteries and veins.

Hemodynamic effects: A reduction in arterial resistance with a resultant increase in cardiac output is consistently found in chronic congestive heart failure patients. The PCWP and therefore pulmonary edema will decrease as stroke volume increases.

Indications: Acute and chronic congestive heart failure due to cardiomyopathy, mitral regurgitation, congenital heart disease, and other etiologies.

How supplied: Captopril 12.5, 25, 50 mg tablet (Capoten, Squibb).
Dosage: 0.5–2 mg/kg po q8–12h (dog); 1/8 - 1/4 of a 25 mg tab q8–12h (cat). A gradual increase in the dose to maintenance levels may reduce the incidence of hypotension, as described for hydralazine.
Side effets and limiting factors: Hypotension and associated signs may occur, especially after the first dose in man. Other reported side effects in man include neutropenia, proteinuria, renal failure, and gastrointestinal signs. Gastrointestinal signs appear to be the most common complications in the dog and cat. The dosage should be lowered in patients with renal disease that is not secondary to heart failure.

Vasodilators not Routinely Administered

1. *Nitroprusside* (6,14,23,26):
Primary effects: An intravenous agent which results in direct relaxation of the smooth muscle in the peripheral vascular bed by unknown mechanisms.
Site of action: A balanced effect on arteries and veins.
Hemodynamic effects: Reduces arterial pressure, arterial resistance, and increases stroke volume and cardiac output. The PCWP, right atrial and pulmonary artery pressures decrease.
Indications: Severe, acute congestive heart failure when the animal is in an intensive care facility.
How supplied: Sodium nitroprusside (Nipride, Roche), 50 mg, powder/ 5 mL vial.
Dosage: 1–5 μg/kg/min IV (dog).
Constant rate intravenous infusion (CRI) calculation (23): bodyweight (kg) × dose (1–5 μg/kg/min) × 0.36 = total dose in mg to administer IV over six hours (add to 5% dextrose in water); (e.g., 20 kg dog, 5 μg/kg/min infusion: (20)(5)(0.36) = 36 mg over 6 hours).
Side effects and limiting factors: Nitroprusside therapy has not been studied in dogs and cats with heart failure. Since it is a potent drug that can easily induce pronounced hypotension, it should only be given in the intensive care facility where arterial blood pressure, PCWP, and CO can be monitored. It has an ultra-short half life and must be given intravenously, which limits its use to acute heart failure. Cyanide and thiocyanate poisoning as well as other severe side effects occur in humans when high, prolonged doses are administered (27).

Summary

Vasodilators should be considered for use in dogs and cats in congestive heart failure, especially if they do not respond adequately to diuretics alone or to diuretics and digoxin. Arterial dilators such as hydralazine or captopril break the vicious cycle in which low cardiac output causes a reflex elevation of systemic vascular resistance (Figure 3). This increased resistance to ventricular ejection further reduces cardiac output. Venous dilators such as the nitrates increase the capacity of peripheral veins to store blood thereby reducing blood volume in the heart and lungs. Consequently, left atrial and ventricular volume and pressure are reduced and dyspnea due to pulmonary edema is relieved. An excessive decrease in left atrial and ventricular volume will result in a decrease in cardiac output. Captopril, an angiotension converting enzyme inhibitor, may be particularly noteworthy because, as well as reducing arterial resistance (afterload) and thereby increasing cardiac output, captopril will reduce the degree of water retention by inhibiting the formation of aldosterone. This drug has proven very effective in relieving signs in many dogs and cats with severe or refractory heart failure.

Although clinical signs and hemodynamic variables often improve with vasodilator therapy, it is not currently known if any of these drugs will prolong survival in animals with chronic heart failure. The dosage and effectiveness of vasodilator therapy must be based on individualized clinical response and, when possible, hemodynamic monitoring of each patient. Hypotension, weakness, and syncope are serious side effects of these agents. CVJ

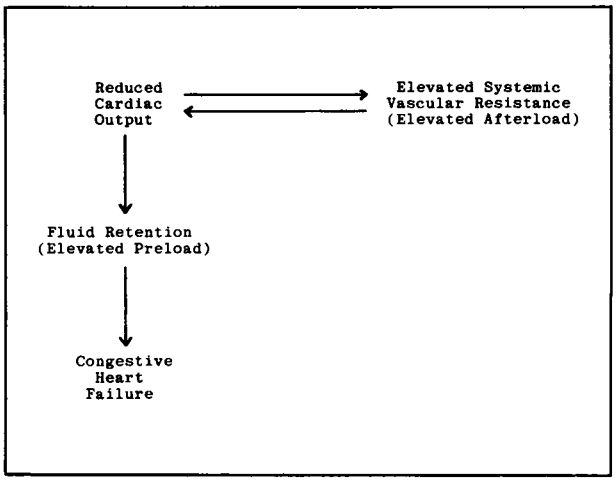

Figure 3. One can readily appreciate how heart failure begets more heart failure.

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