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Advancing Science for Pet Health

TRANSFORMING HEART HEALTH:

A Novel Dietary Intervention For Dogs With Early Stage Myxomatous Mitral Valve Disease

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Heart disease is one of the most common disorders of dogs, affecting one in ten canine patients seen in primary care practice.[1] The most common cause of acquired canine heart disease is myxomatous mitral valve disease (MMVD).

In this cardiac condition, the mitral valve progressively degenerates, leading to an enlarged left atrium and ventricle, a less efficient heart, and the risk of congestive heart failure.

Although the majority of dogs with MMVD are not—and never will be—in heart failure, about 30% develop advanced heart disease.[2-4] The progression to heart failure carries a much poorer prognosis and diminishes a dog's quality of life. An intervention that may provide benefit when dogs are in the early stages of MMVD could help these dogs live better, longer lives.

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HEALTHY HEARTS NEED A CONTINUOUS ENERGY SUPPLY

A dog's heart may beat up to a billion times during their life.[5] Keeping the heart pumping under constantly changing conditions—at rest, while running, in sickness and in health—requires a continuous supply of energy, in the form of adenosine triphosphate (ATP).

The heart cannot store energy for future use. If ATP production suddenly stopped, the heart could only contract for about 12 more beats.[6]

To meet these high-energy demands, every cardiomyocyte contains thousands of mitochondria, the cellular factories for energy production.[7,8]

The healthy adult mammalian heart typically derives up to 90% of ATP from the oxidation of long-chain fatty acids.[6,9]

However, mitochondria have the metabolic flexibility to use different energy substrates to meet ATP demands depending on cardiac workload, availability of the energy sources, or the nutritional state of the animal.

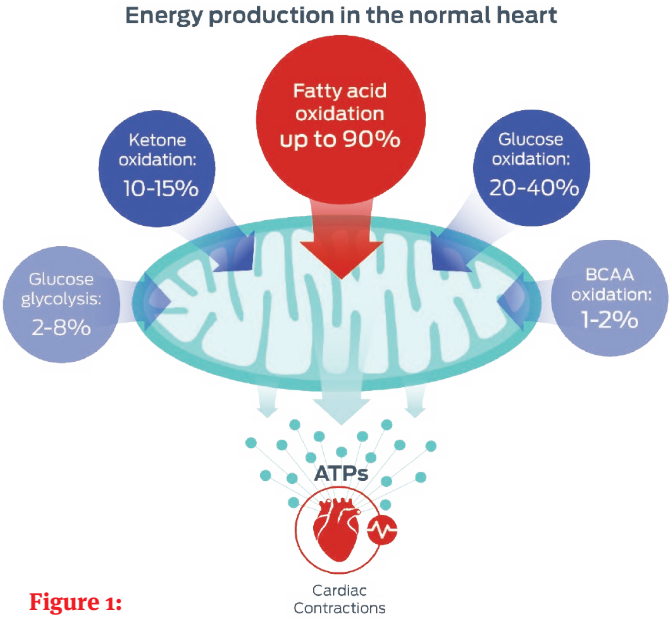


Figure 1:
Long-chain fatty acids are the primary energy substrate in the healthy mammalian adult. The remaining energy comes from the oxidation or glycolysis of glucose, and other energy sources.[6,9,10]

The failing heart: An energy crisis

Heart disease refers to cardiac pathology—regardless of whether it affects the heart muscle, valves, or metabolism. However, heart failure refers to clinical signs—such as fluid accumulation in the lungs or abdomen—that occur when the heart is unable to compensate for changes associated with the heart disease.

Heart disease does not always lead to heart failure. The prognosis depends on the disease, its rate of progression, and the dog's overall health.[1] For example, in one retrospective study of more than 500 dogs, 70% of dogs with mitral valve disease did not progress to heart failure. However, about 30% progressed to a worse stage of heart disease over several years: 18% of dogs with MMVD developed symptomatic heart failure within one year and about 11% of asymptomatic dogs died from heart failure within 5 years.[2]

In failing hearts, compromised energy metabolism is a critical factor.[6,10,11] A brief look at how the heart meets its energy needs reveals how nutrition could play a pivotal role in managing heart disease.

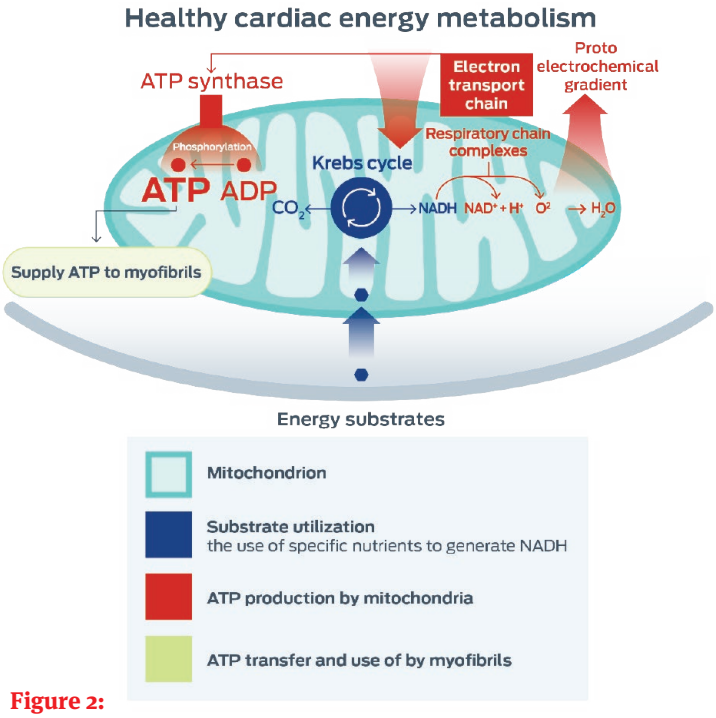


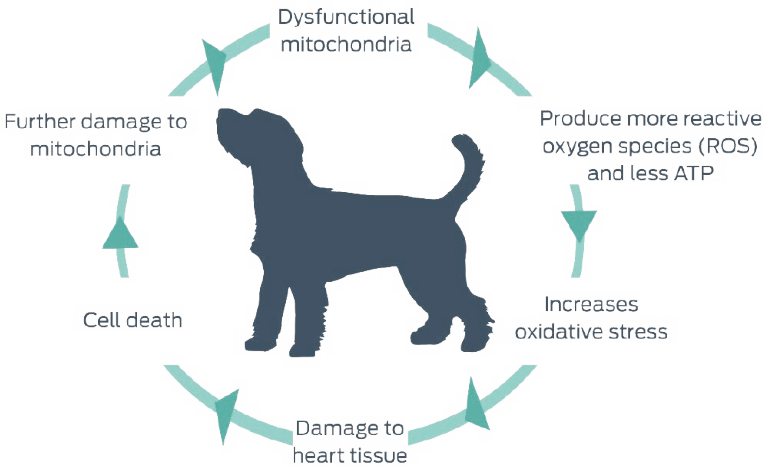
Figure 2:
Mitochondria convert the chemical energy stored in fatty acids, glucose and other substrates, into ATP that fuels the heart's contractions. Failure to produce an adequate amount of energy leads to mechanical failure of the heart. [Adapted from Neubauer 2007]

In general, cardiac energy metabolism has three components[10]:

- the use of specific substrates to generate energy
- ATP production by mitochondrial oxidative phosphorylation
- transfer of ATP within the heart muscle cells (myofibrils)

Studies in animals and people show changes can occur in any—or all—of the three components of cardiac energy metabolism: substrate utilization, oxidative phosphorylation, or ATP metabolism.[12]

If adverse health conditions cause mitochondria to become dysfunctional, then ATP production becomes less efficient. With less energy to fuel muscle contraction, the heart becomes less effective.



Dysfunctional mitochondria also produce more reactive oxygen species (ROS), which increases oxidative stress and leads to cell damage. This can lead to a cycle of progressively inefficient energy production.[9,10,12-15]

Insights from studies using omics technologies

Studies in both people and animals have shown that gene expression and metabolite profiles associated with energy metabolism differ significantly between healthy hearts and diseased hearts.[16-20]

Purina scientists applied metabolomics and transcriptomic technologies to better understand the molecular-level changes that occur in dogs with early stage MMVD.[18]

Among the key changes identified in this multi-omics study, the scientists found:

- 54 serum metabolites were significantly different between healthy and MMVD dogs
- More than 1,000 gene transcripts in mitral valve and left ventricular tissue were differentially expressed

These changes represented altered pathways associated with:

- energy metabolism and bioenergetics
- oxidative stress
- inflammatory mediators
- extracellular matrix homeostasis

Additionally, gene expression and metabolite levels for glucose metabolism and anaerobic glycolysis were increased, indicating that in dogs with MMVD, their hearts were using less efficient ATP production pathways that are not typically used by a healthy heart.

Similar to findings in studies of human heart failure,[6,9,10] these changes suggest that cardiac metabolism in dogs with MMVD shifts away from using long-chain fatty acids as a primary substrate for energy. The process of energy production becomes less efficient overall.

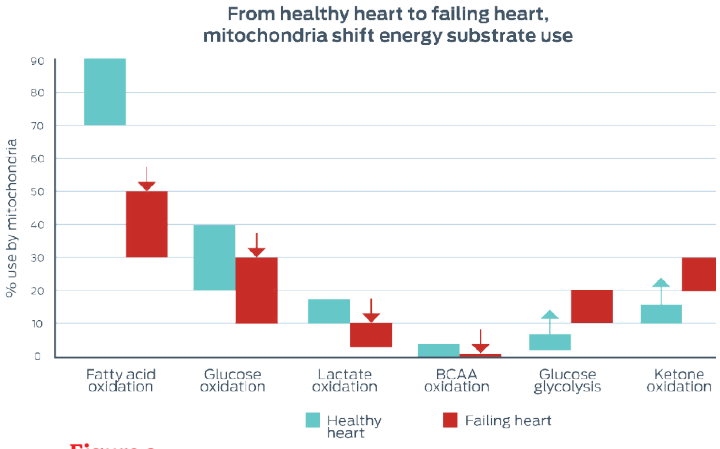


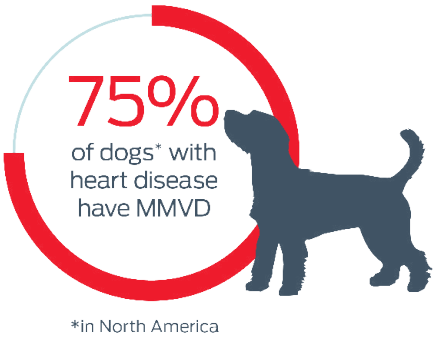
Figure 3:
This graph depicts the shift in energy sources used by mitochondria in the failing heart.

These altered bioenergetics offer insights into possibilities for nutritional interventions. Research suggests that nutrients providing alternative energy sources, and addressing other metabolic changes found in MMVD, could transform the management of cardiac health.

MYXOMATOUS MITRAL VALVE DISEASE (MMVD)

Understanding MMVD

Myxomatous mitral valve disease is the most common canine heart disease, accounting for approximately 75% of acquired heart disease in dogs.[1,21-23] The highest incidence occurs in older, small- to medium-sized dogs weighing less than 20 kilograms.[1,24]



Small dog breeds such as Miniature Poodles, Dachshunds, Yorkshire Terriers and Whippets are predisposed to MMVD, and nearly 100% of Cavalier King Charles Spaniels develop this cardiac condition.[25,26] A few large breed dogs, such as German Shepherds and Doberman Pinschers, may also have this valve disease.[2]

The mitral valve maintains a one-way blood flow from the left atrium to the left ventricle. With myxomatous degeneration, nodules form along the edges of the normally thin and translucent valve. As MMVD progresses, the valve tissue thickens and no longer forms a tight seal when the heart contracts. This "leaky" seal allows blood to regurgitate into the left atrium.

With time, the degenerating valve and increasing mitral regurgitation lead to left atrial enlargement, compensatory left ventricular remodeling and heart failure. About 30% of dogs with MMVD also have tricuspid valve insufficiency.[27]

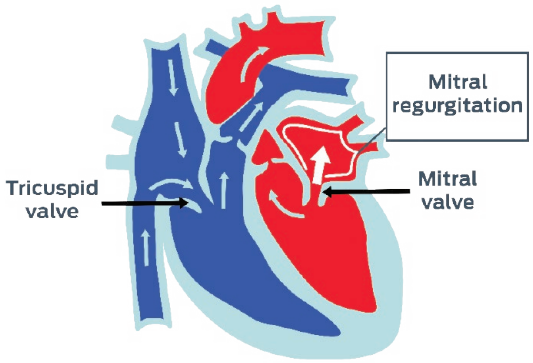


Figure 4:
With MMVD, the mitral valve progressively thickens and becomes less effective at maintaining the one-way flow of blood from the left atrium to the left ventricle. This mitral regurgitation leads to remodeling of the heart and, eventually, the risk of heart failure.

At the molecular level, a key step in the development of MMVD is the transformation of specific cells in the extracellular matrix of the valve. Studies show that valvular interstitial cells (VICs) change into active myofibroblasts, disrupting the flexible structure (and function) of the valve.[28] The mechanism behind these changes is not yet known, but serotonin (5-hydroxytryptamine or 5HT) appears to have an important role in the pathogenesis of the disease. Better understanding how serotonin helps trigger VIC activation may lead to improved MMVD management in the future.[29,30]

The list of synonymous terms for MMVD reflect the array of changes that occur in this disease.[2,27]

- Mitral valve disease (MVD)
- Degenerative mitral valve disease (DMVD)
- Chronic mitral valve insufficiency (CMVI)
- Atrioventricular valve disease (AVD)
- Chronic valvular disease (CVD)
- Atrioventricular valvular insufficiency (AVVI)
- Endocardiosis
- Chronic valvular endocarditis
- Valve fibrosis
- Mucoid degeneration

The diagnosis of subclinical MMVD is based on auscultation and signalment. In most dogs the heart disease will be discovered when a left apical systolic murmur is auscultated during a routine exam.[1,31] Further diagnostics may include thoracic radiography to obtain a baseline vertebral heart score (VHS), assess heart size, and evaluate any pulmonary changes.

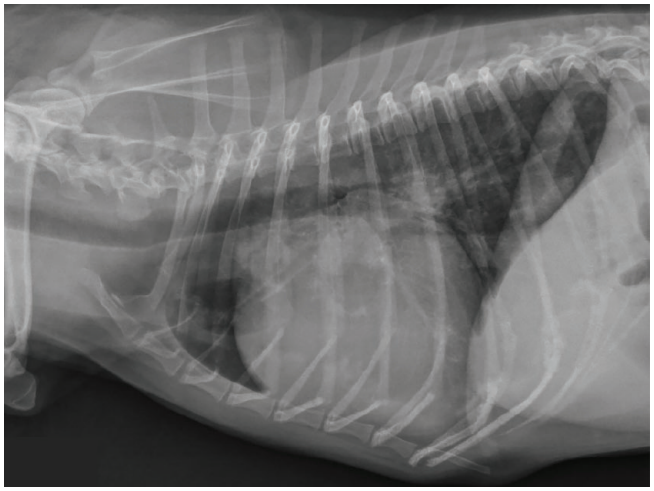


Figure 5:

Right lateral thoracic radiograph of a dog in ACVIM stage B2 MMVD
Image courtesy of: Rebecca Stepien, DVM, MS, DACVIM (Cardiology)
University of Wisconsin, USA

Although recent studies show that radiographs can confirm a diagnosis of MMVD[32], the echocardiogram is still considered the gold standard for evaluating cardiac structure and function.

According to consensus guidelines of the American College of Veterinary Internal Medicine (ACVIM), dogs with MMVD are classified into one of four stages based on clinical findings and echocardiographic evaluation. This staging scheme was developed, and updated, by a panel of veterinary cardiologists to link the severity of morphologic heart changes and clinical signs with appropriate treatments for each stage.[1,24]

ACVIM CLASSIFICATION SCHEME FOR MMVD

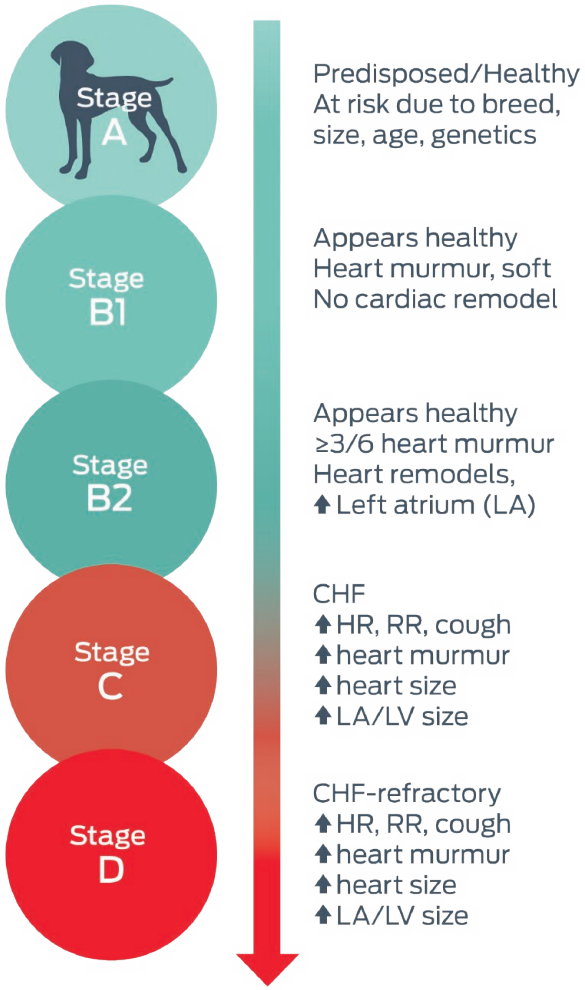


Figure 6:

The ACVIM consensus guidelines for staging dogs with MMVD were adapted from functional classification systems for heart disease in people and dogs, including systems developed by the New York Heart Association (NYHA) and the International Small Animal Cardiac Health Council (ISACHC).

Compared to early stage dogs with MMVD, those with signs of congestive heart failure (CHF) have a much shorter survival time.[32-37]

Heart failure is the third most common cause of death in dogs.[38]

Once dogs experience clinical heart failure, the goals are to manage clinical signs, delay further progression and maintain quality of life. Most dogs receive some combination of medical therapy with diuretics, angiotensin-converting enzyme (ACE) inhibitors, aldosterone receptor blockers, and/or positive inotropes.[1,24,39]

Dietary management recommendations for dogs with MMVD currently target later stages of disease, after heart failure occurs, and are focused on controlling clinical signs.

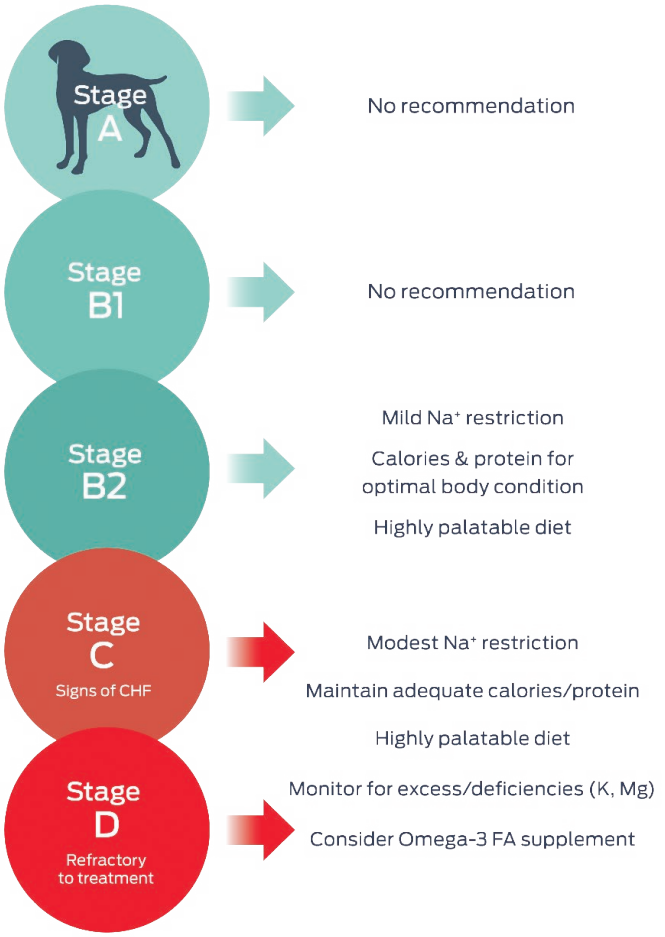


Figure 7:
This diagram highlights the current ACVIM recommendations for the nutritional management of dogs with MMVD.[1]

These recommendations include:

- maintaining protein and calorie intake
- monitoring potassium levels due to losses from diuretic medications
- moderately restricting sodium intake to mitigate fluid accumulation

Although studies in people have linked high salt intake with high blood pressure and, in turn, negative impacts on heart health, studies have not shown that sodium has a role in causing heart disease in dogs. Excessive restriction of sodium should be avoided as it stimulates aldosterone activation, which can have adverse effects.[40] Moderate sodium restriction, however, can help manage symptoms of fluid overload in heart failure. (Reduced cardiac output in heart failure stimulates the renin-angiotensin system and leads to increased fluid retention.)[41-44]

Diet palatability is also an important nutritional factor. Cardiac cachexia is common in dogs with CHF, and is associated with significantly shorter survival times.[45-47] Omega-3 fatty acids are also recommended to help reduce inflammation, which may be important in cachexia.[45,48-51]

All of these recommendations are aimed at reducing the workload of the failing heart and managing clinical signs.

Progression of MMVD

The rate of progression from one stage of MMVD to the next is variable and hard to predict. However, the prognosis is more favorable for dogs in early stage stages of MMVD, without signs of congestive heart failure (CHF).[1,34,52]

Numerous studies describe potential biomarkers for predicting the progression of MMVD. Identifying prognostic factors that are easily obtainable by testing a blood sample could aid veterinary practitioners when managing dogs with MMVD, and help inform dog owners of the likely outcome for their pet.[53]

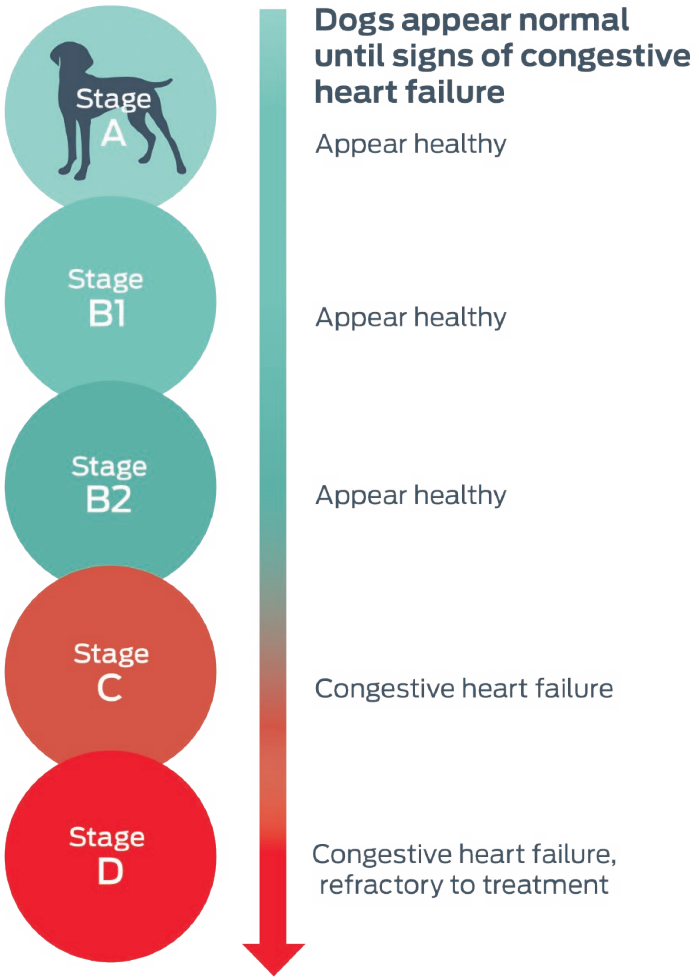


Figure 8:

Based on the ACVIM classification scheme for dogs with MMVD, dogs show no clinical signs until they experience congestive heart failure.

Two biomarkers with some demonstrated value for MMVD dogs are: N-terminal pro b-type natriuretic peptide (NT-proBNP) and cardiac troponin I (cTnI).

NT-proBNP is a marker of myocardial wall stress secondary to volume or pressure overload. This naturetic peptide has been shown to help differentiate CHF from primary respiratory diseases.[54-57] Studies show that NT-proBNP may also have prognostic value in early stage MMVD.[53,58,59]

Cardiac troponins are released into the bloodstream after injury to heart muscle cells. They are sensitive and specific markers of cardiac injury from any underlying cause. Studies show that plasma levels of cTnI are abnormally increased in dogs with moderate and severe MMVD, and cTnI concentration is negatively associated with prognosis. However, this marker is most strongly associated with all-cause mortality, not cardiac-specific causes.[53,60-64]

Many factors are associated with the progression of MMVD, including: age, gender, intensity of heart murmur, degree of valve prolapse, severity of valve lesions, the degree of mitral valve regurgitation, degree of left atrial enlargement, severity of eccentric hypertrophy, and rupture of chordae tendinae.[3,21,25,34,57,65]

Of these factors, the degree of left atrial enlargement (LAE) appears to be the most consistent indicator of progression.[39,66,67]

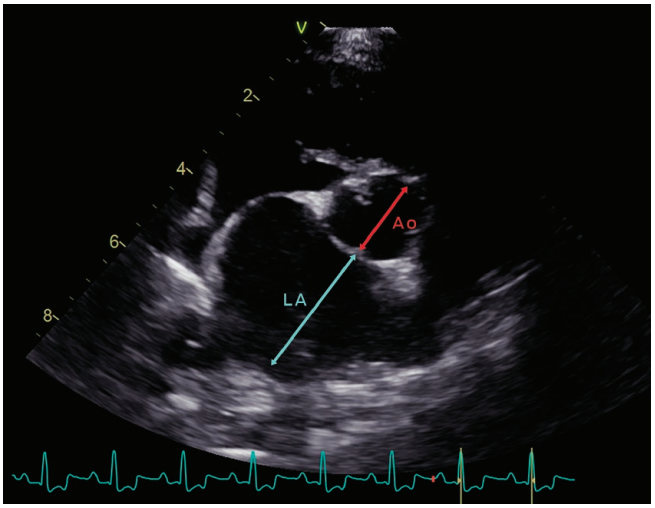


Figure 9:

Echocardiographic measurement of left atrial diameter (LA) and aortic root (Ao) Image courtesy of: Rebecca L. Stepien, DVM, MS, ACVIM (Cardiology) University of Wisconsin, USA

LAE is evaluated by the ratio of left atrial diameter to aortic root diameter (LA/Ao), as measured by echocardiography.

Once progression occurs, a dog's lifespan and quality of life diminish. The goal, therefore, is to slow or prevent progression of MMVD.

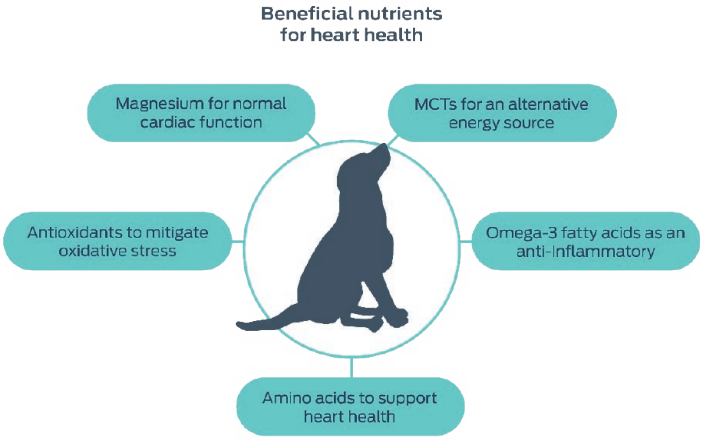
Owners rate quality of life better than quantity for dogs in heart failure.[68]

NUTRITIONAL BREAKTHROUGH STUDIES FOR DOGS WITH EARLY STAGE MMVD

While studies have shown the beneficial roles for many nutrients in heart health, nutrition is often overlooked in the management of heart disease. Purina scientists developed a blend of nutrients that could address key metabolic changes they previously identified in dogs with MMVD.

Identification of specific nutrients with cardiac protection benefits

Based on insights from previous omics research, Purina scientists formulated **a cardiac protection blend (CPB) of nutrients that includes medium-chain triglycerides (MCTs) as an alternative energy source, omega-3s to help reduce inflammation, Vitamin E and other antioxidants, together with key amino acids and minerals important for cardiac health and function.**



Long-chain fatty acids are the primary substrate used by healthy cardiac mitochondria to generate energy. In heart disease, energy metabolism becomes less efficient—particularly regarding long-chain fatty acids.[9,10,69]

MCTs are readily hydrolyzed to medium-chain fatty acids (MCFAs), which provide a more available substrate for cellular energy.

With a shorter carbon chain, MCFAs provide a more available source of energy because they do not require membrane transporters for uptake into cells and mitochondria.[70,71] In contrast, long-chain fatty acids need carnitine cofactors for transport into the mitochondria.[72]

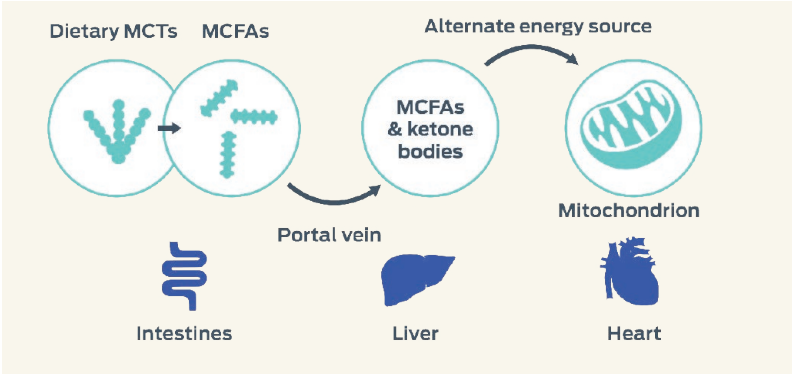
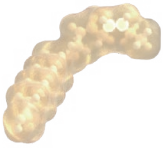
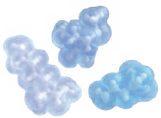


Figure 10:
Dietary medium-chain triglycerides (MCTs) can provide an alternative energy source for cardiac mitochondria. MCTs are metabolized into MCFAs, which do not need transporters to enter mitochondria for ATP production.

Studies also show that MCTs reduce mitochondrial and cytoplasmic ROS, and can have a favorable impact on cardiac disease progression.[70,73,74]



The long-chain **omega-3 fatty acids, especially eicosapentaenoic acid (EPA), have demonstrated numerous cardiac benefits.** Studies show that omega-3s from fish oil help reduce inflammatory mediators and oxidative stress, stabilize cardiac arrhythmias in dogs, reduce blood pressure, and reduce cardiac remodeling.[49, 75-80]



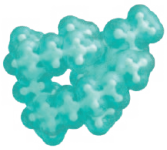
Taurine is the most abundant amino acid in heart tissue. While it is not an essential nutrient for dogs, studies have shown that taurine has a key role in maintaining heart muscle contractility and homeostasis.[81-83] Research has also linked deficiencies to the development of heart disease.[81]

Low taurine levels have been associated with decreases in the sensitivity of cardiac muscle to calcium and the loss

of myofibrils.[83-85] While the exact mechanism for taurine deficient cardiomyopathy is still not known, taurine-responsive heart disease has been reported in breeds including: the American Cocker Spaniel, Golden Retrievers, Doberman Pinschers, and Newfoundlands.[81]

Lysine and methionine are amino acid precursors for the biosynthesis of carnitine, a peptide which helps transport LCFAs acids into the mitochondria.[86, 87]

Vitamin E is a well-established antioxidant, has anti-inflammatory properties, and can also influence gene expression in ways that help prevent heart disease.[86,88,89]



As an antioxidant, Vitamin E scavenges free radicals by either preventing their formation or removing them before they can cause damage.

While free radicals are a consequence of normal cell metabolism, if these ROS are not adequately cleared then oxidative stress occurs. Increasing oxidative stress leads to cell membrane damage, DNA damage and protein denaturation.

Studies show that antioxidants may be even more important in heart disease because levels of ROS increase under conditions of mitochondrial dysfunction—a key feature of heart failure.[90-93]

One recent study showed that superoxide dismutase activity, a common free radical scavenger, gradually decreased in dogs with advanced stages of mitral valve disease.[94]

Magnesium is a mineral proven to play multiple roles in maintaining healthy heart function. In heart cells, it complexes with ATP to deliver this molecular energy outside the mitochondria. Among its roles, magnesium provides antiarrhythmic action and acts as an antioxidant. In people, inadequate levels of magnesium correlate with heart failure and increased risk for cardiovascular disorders.[95-98]

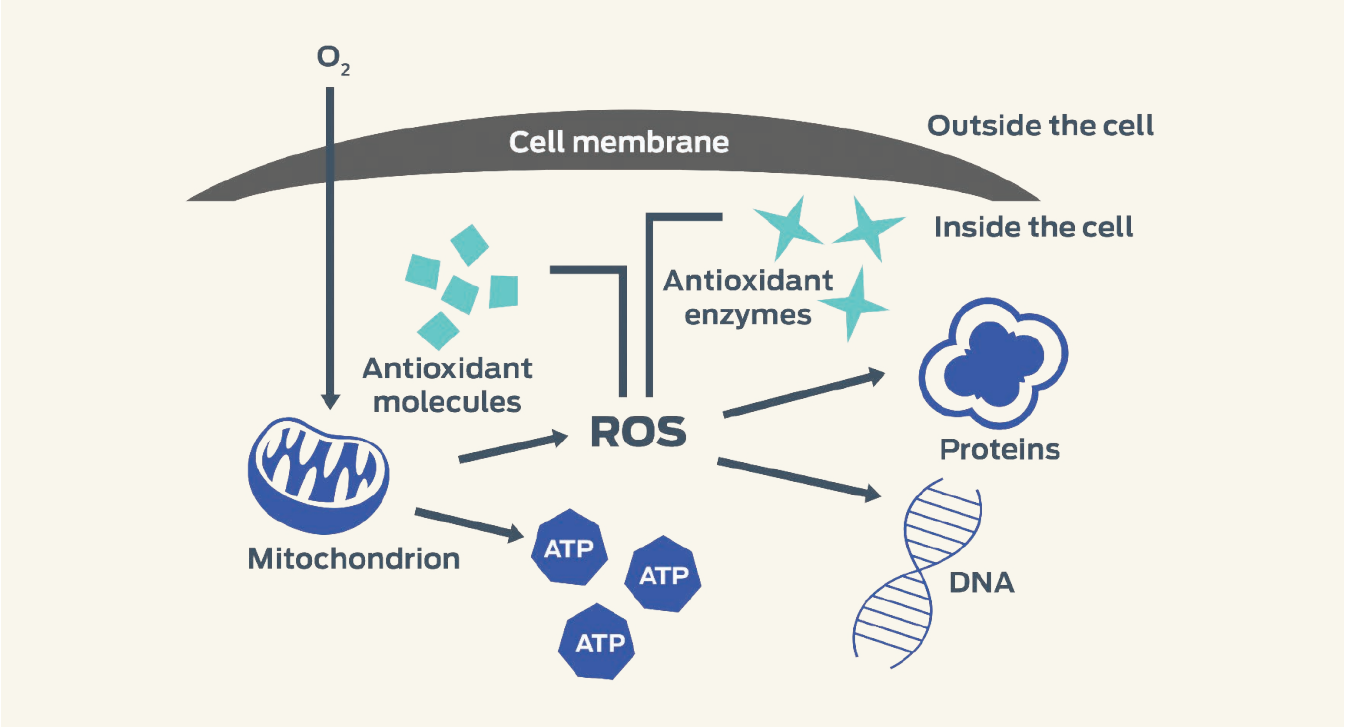


Figure 11:

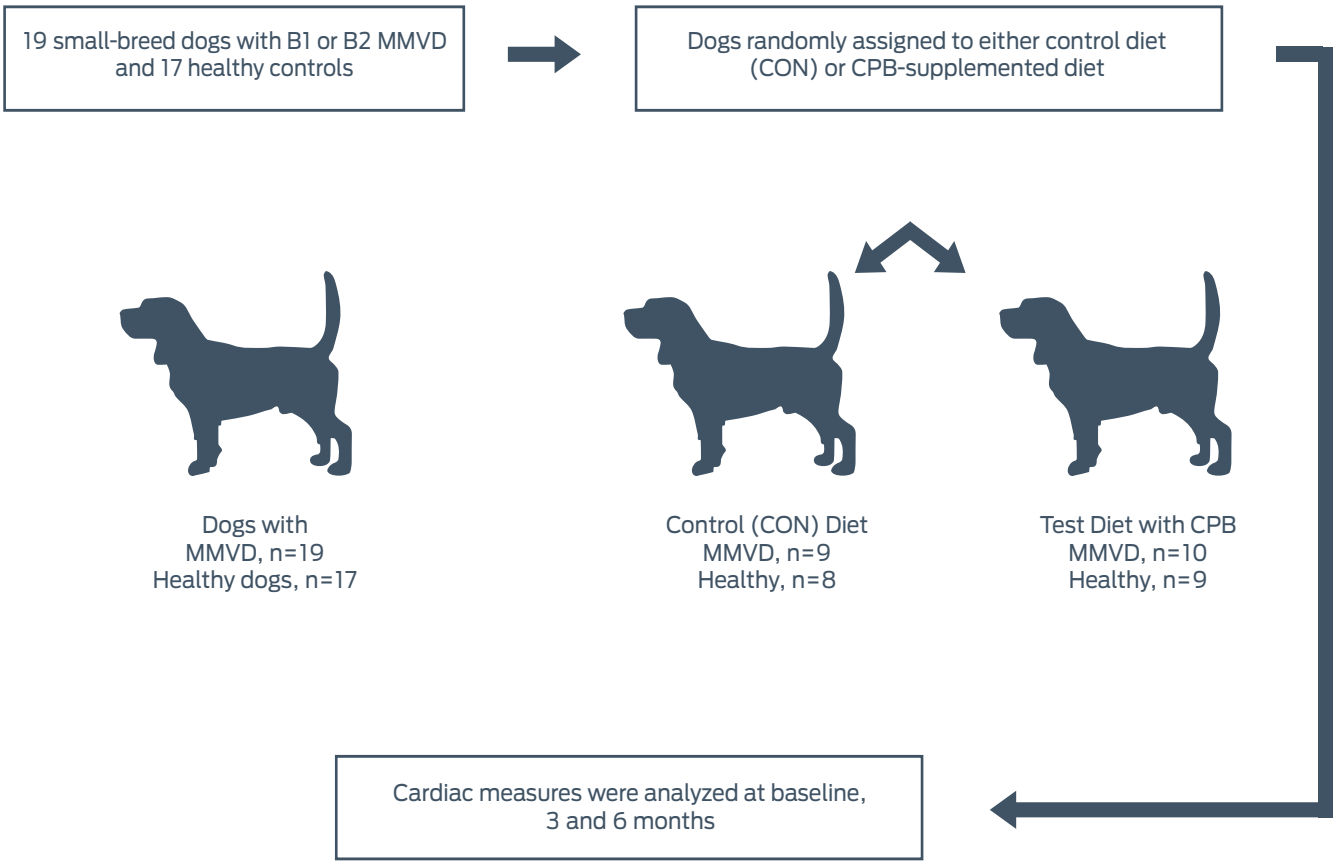
Antioxidants can reduce the impact of reactive oxygen species (ROS) and prevent damage to cell proteins, cell membranes or DNA.

Internal dietary study with dogs with early stage MMVD fed a diet containing a cardiac protection blend (CPB)

In a six-month, placebo-controlled, dietary intervention study, the dogs consuming the CPB-supplemented diet showed changes suggesting the specific blend of nutrients may help improve heart function in dogs with stage B1 and B2 MMVD.[99]

This blinded, randomized feeding trial enrolled 19 dogs in stage B1 or B2 heart disease. The dogs were divided into two groups randomized by age, sex, breed, body weight, and murmur grade, then fed a complete and balanced diet that was either a control diet (CON) or the CPB-supplemented diet. Any dogs on cardiac medications prior to enrollment were maintained on the same medications throughout the study. All dogs were evaluated with echocardiography at three time points: baseline, three months and six months.

Although MMVD is a variably progressive heart disease, the dogs fed the CPB-supplemented diet showed echocardiographic changes suggesting that the CPB may help slow the progression of early stage MMVD. The dogs eating the CPB-supplemented diet had average decreases in echocardiographic variables (LAD and LA/Ao), and fewer dogs progressed from stage B1 to stage B2 versus the control group.



Metabolomics: Connects clinical benefits of the CPB nutrients with cellular-level changes

In follow-up research, Purina scientists analyzed serum metabolites of dogs in the dietary study.[100]

Among more than 100 differential metabolites, the results showed that clinical benefits demonstrated during the dietary study were also associated with positive changes at the metabolic level:

- improved fatty acid use and bioenergetics
- reduced markers of inflammation
- reduced oxidative stress

Significant metabolite changes in CPB group	Impact on heart health
↑ 2.7-fold increase in alpha-aminobutyrate	Modulates glutathione balance; glutathione protects against oxidative stress, especially in the heart.
↑ 2-fold increase in arginine and citrulline	These amino acids are precursors for nitric oxide biosynthesis. Nitric oxide acts mainly against oxidative stress and helps optimize cardiac pump function.
↑ 3-fold increase in caprate	This is a 10-carbon, medium-chain fatty acid (MCFA). MCFAs from MCTs are sources of energy that get directly into mitochondria. They do not need special transporters or pathways that use carnitine.
↑ 2.5-fold increase in deoxycarnitine	An amino acid that is the immediate precursor of carnitine biosynthesis. Carnitine's prime function is to shuttle long-chain FAs to the mitochondria for energy production.
↑ ceramides and sphingomyelins with very long-chain fatty acids	Research in humans has shown decreased risk of heart failure when ceramides and sphingomyelins were increased with VLCFAs.
↓ margarate and methylpalmitate	These FAs correlated with changes in left atrial diameter—a key measure of MMVD progression. Dogs with lower margarate and methylpalmitate showed less expansion of left atrial diameter, so less progression of MMVD.
↓ greater decrease in ratios of omega-6 to omega-3 fatty acids	Inflammation plays an important role in cardiovascular disease. Omega-3 FAs such as eicosapentaenoic acid have key anti-inflammatory/anti-aggregatory effects while omega-6 FAs, such as arachidonic acid, are generally pro-inflammatory.
↓ Acylcarnitines: oleoylcarnitine, adipoylcarnitine, and margaroylcarnitine	Suggests an improvement in cardiac fat utilization.

This sequence of studies suggests that dietary intervention, with a blend of specific nutrients chosen to address key metabolic changes identified in dogs with MMVD, may help slow the progression of early stage MMVD.

Balanced nutrition has always played a key role in maintaining heart health. Now, a novel nutritional approach offers clinical benefits for dogs with early stage MMVD. Studies demonstrate that a unique blend of nutrients may help improve heart function in dogs with stage B1 and B2 MMVD.

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